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DISEASES OF CHILDREN

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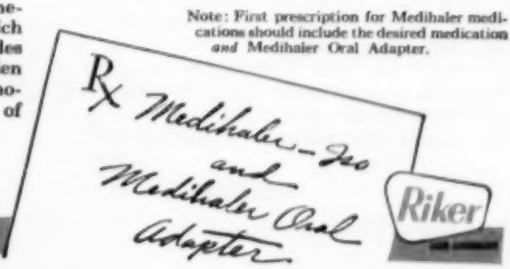

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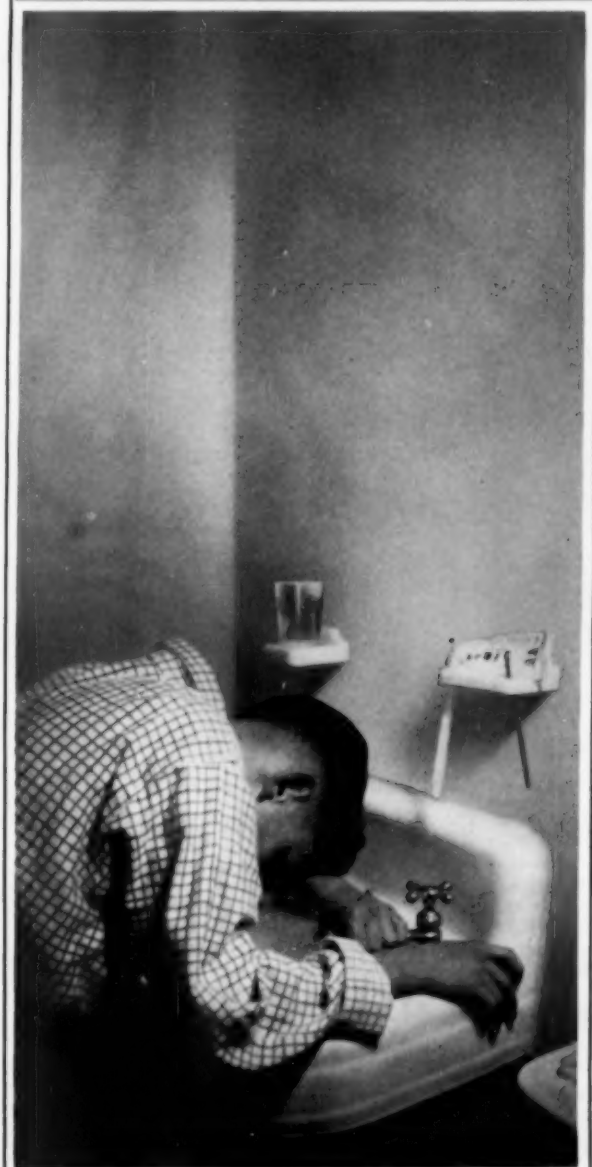

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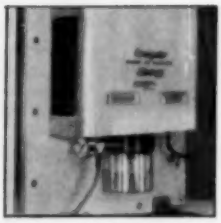

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(1) Diamond, L. K.; Smith, N. J., and Vaughan, V. C., III, in Nelson, W. E.: Textbook of Pediatrics, ed. 6, Philadelphia, W. B. Saunders Company, 1954, p. 962. (2) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86:553, 1953.

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DISEASES OF CHILDREN

Luteinized Cysts in Ovaries of Infants Born of Diabetic Mothers

ROBERT C. AHLVIN, M.D., and WALTER C. BAUER, M.D., St. Louis

Follicular cysts are frequently found in the ovaries of newborn infants; however, luteinization of the theca interna of the cysts has been rarely reported.[1] The recent observation of this phenomenon in an infant born of a diabetic mother stimulated us to search our autopsy series for other examples of this association.

Materials and Methods

The autopsy protocols of the Department of Pathology of Washington University School of Medicine from 1910 to 1955 were examined and of these 17,500 autopsies eight newborn girls born of diabetic mothers were found. Microsections or suitably preserved tissue for this study were available from five of these infants, and they comprise the basis of this study. In addition, ovaries taken at the time of autopsy of 92 newborn girls were selected consecutively from our autopsy files from 1942 to 1952 to serve as a control group.

The ovaries were imbedded in paraffin, sectioned, and stained with hematoxylin and eosin, and a single longitudinal section taken approximately through the midpoint of the ovary was examined. In 88 cases both ovaries were examined.

Follicular cysts were present in 44 of the 92 cases in the control group. When present in one ovary in a particular case they were present with few exceptions in the other ovary. Rather large polygonal cells with abundant lacy eosinophilic cytoplasm were occasionally seen in the theca interna of these cysts. For the purposes of this study, this change was not interpreted as luteinization, but rather this term (luteinization) was reserved for those cysts whose walls were composed almost entirely of vascular spaces and luteinized cells (Figs. 1, 2). Using this criterion it was possible to separate all the ovaries into two groups depending on whether or not luteinized cysts were present.

Submitted for publication July 6, 1956; accepted Aug. 12.

From the Department of Pathology, Washington University School of Medicine.

Results

Luteinized cysts were found in three of the five newborn infants (60%) born of diabetic mothers (Table). When present they were bilateral. The number of cases in this group is regrettably small, and therefore the significance of the finding is difficult to assess; nevertheless the incidence of luteinized cysts is much higher in the infants born of diabetic mothers than in the control group

Fig. 1.—Ovary of an infant born of a diabetic mother showing several follicular cysts surrounded by luteinized theca interna cells. Hematoxylin and eosin, × 30.

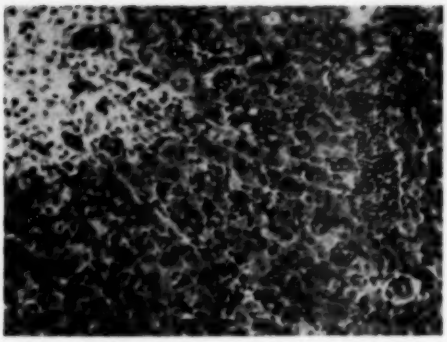

Fig. 2.—Broad band of luteinized theca interna cells in ovary of an infant born of a diabetic mother. Note the cord-like arrangement of cells, abundant lacy cytoplasm, and congested vascular spaces. Loose vascularized connective tissue fills the cyst lumen at the upper left. Hematoxylin and eosin, × 180.

where they were present in 7.5% of the cases and the difference in incidence is statistically significant ($P<0.01$).

Comment

Reports of luteinized ovarian cysts in newborn infants have appeared sporadically in the literature. Hamilton [2] reported two girls born of diabetic mothers, and in one of these luteinized cysts were seen. Smyth and Olney [3] published a similar case in which the ovaries were extremely large and cystic with lutein change of the thecal cells. Potter [1] illustrates the phenomenon with a photomicrograph of an ovary from an infant who weighed more than 5000 gm. (11 lb.) at birth. This high birth weight is suggestive of the prediabetic state in the mother or maternal diabetes,[4,5] although no maternal history is given. Benner [6] reports a case of an infant whose ovaries had many large polygonal cells resembling theca lutein cells surrounding many follicular cysts and also diffusely spread through the ovarian stroma. There was a history of maternal diabetes in this case also.

Luteinized Ovarian Cysts in Newborn Infants

	No. Cases	With Luteinized Cysts	%
Newborn infants with maternal diabetes	5	3	60.0
Newborn infants without maternal diabetes	92	7	7.5

x-Square, 14.7; P <1%.

Luteinization of the theca interna in infants is not unique to those born of diabetic mothers as is shown in our control group. Govan and Mukherjee [7] carefully examined, by serial section, the ovaries of 25 stillborn infants with maternal toxemia and found luteinized cysts in 7. Luteinized cysts were not seen in their 29 control infants who were similarly examined. The hospital records of the infants in our control group who were found to have luteinized ovarian cysts were reviewed and a history of maternal toxemia was found in only one case. Because of the nature of the material available no statement can be made as to whether maternal diabetes or toxemia is most frequently associated with this phenomenon, but in any event neither were present in six of our cases.

There were eight erythroblastotic infants in the control series and of these one was found to have luteinized follicular cysts. This is an incidence of 13% and is not significantly different from the incidence in the control group. There were two infants in the control group whose pancreatic islets appeared hypertrophied microscopically and in whom no history of maternal diabetes or evidence of erythroblastosis was present. Neither of these infants had luteinized cysts.

The age of the fetus does not appear to play a dominant role in the production of this change, as one of the infants in the diabetic group who had luteinized cysts was premature, weighing only 1900 gm. It is of interest that this infant was an anencephalic monster in whom no pituitary remnant was found. The smallest infant in the study who had luteinized follicular cysts was in the control group, and this infant weighed 1700 gm.

Summary and Conclusion

The ovaries of five newborn infants born of diabetic mothers are examined and luteinized follicular cysts are found in three. Luteinized cysts are also found in the ovaries

of 7 out of 92 newborn infants used as controls. One of these cases is associated with maternal toxemia and another with maternal Rh incompatability. The incidence of leutenized follicular ovarian cysts is higher in infants with a history of maternal diabetes than in a large control group.

Department of Pathology, Washington University School of Medicine, Euclid Ave. and Kingshighway.

REFERENCES

1. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, Year Book Publishers, Inc., 1952, p. 396.

2. Hamilton, G. M.: Ovarian Cysts in the Newborn Infant of Diabetic Mother, J. Obst. & Gynaec. Brit. Emp. 60:533-534, 1953.

3. Smyth, F. S., and Olney, M. B.: Diabetes and Pregnancy: Observations on Offspring with Pathologic Report, J. Pediat. 13:772-786, 1938.

4. Hoet, J. P.: Liver and Carbohydrate Metabolism, Liver Injury, in Conference on Liver Injury, Tr. Twelfth Conf., Josiah Macy, Jr. Foundation, edited by F. W. Hoffbauer, New York, Corlies, Macy and Co. Inc., 1953, p. 35.

5. Miller, H. C.: Effect of Diabetic and Prediabetic Pregnancies on Fetus and Newborn Infant, J. Pediat. 29:455-461, 1946.

6. Benner, M. C.: Stimulation of Gonads Associated with Hyperinsulinism in an Infant, Arch. Path. 32:818-824, 1941.

7. Govan, A. D. T., and Mukherjee, C. L.: Maternal Toxaemia and Foetal Ovarian Activity: Preliminary Observations, J. Obst. & Gynaec. Brit. Emp. 57:525-529, 1950.

A Previously Unreported Acute Exanthem Resembling Scarlet Fever

MARY D. AMES, M.D., Harrisburg, Pa.

The purpose of this paper is to describe an apparently new disease entity and to discuss the importance of its proper diagnosis. The cases in this study were seen at the State Hospital for Crippled Children, Elizabethtown, Pa., from Nov. 4, 1955, to April 4, 1956. This hospital is an orthopedic hospital which admits children from birth to 21 years of age for correction and rehabilitation of either congenital or acquired skeletal deformities. The census averages 150, and the children are divided into six open wards according to sex and age. There is free intermingling in the wards, at school, in physiotherapy, hydrotherapy, and occupational therapy. The immediate pre- and postoverative children are segregated in two- or four-bed wards.

During the five months from Nov. 4, 1955, to April 4, 1956, twenty-three orthopedic patients, two house officers, two nurses, and the wife and two children of one of the house officers were infected with this disease. The total cases were 30.

This entity occurred in children from 4 to 12 years of age and in five adults, four of whom were closely associated with them. The sex incidence was 3:2 females to males.

The method of spread and the period of incubation were hard to determine. After the first two cases, the children were not isolated and the cases were rather spotty in the four wards with girls and boys from 4 to 12. Surgery was not discontinued and there were no cases in these wards, although the resident physicians handled both groups of children. The wife and two children of one of the physicians who had the disease did not become ill for six weeks, when they all succumbed together. The family of the other physician who had the disease was not infected and a small nephew of a third adult broke out in a rash 48 hours after apparent exposure. All orthopedic patients had been in the hospital from two months to six years, except for one patient who had been in routine admission isolation for the four days prior to the eruption of his rash.

The three constant manifestations of this disease were fever, sore throat, and a generalized, diffuse, finely papular, bright-red erythema. This erythema was present over the entire body, neck, and extremities but was particularly marked in the inguinal regions and over the anterior trunk. There was no desquamation.

The onset was abrupt with a temperature which ranged between 100.4 and 103 F, sore throat, general malaise, followed in 12 to 48 hours by the appearance of the rash. The temperature remained elevated until 36 to 48 hours after the appearance of the eruption. Nausea and vomiting were present in 17 cases, and, of these, 2 required intravenous therapy. Abdominal pain was present in 20, and signs of an upper respiratory infection in four. There was no lymphadenopathy. The children were not remarkably ill and continued to be alert and active, whereas the adults were incapacitated for 24 to 48 hours with marked malaise and weakness.

The throat was a beefy red with the posterior pharynx edematous and covered with a mucopurulent exudate. The uvula and the soft palate were also edematous and were dotted with petechiae. The tongue was moderately coated and swollen and in several

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cases it was described in the record as a "strawberry tongue."

Laboratory studies revealed white blood cell counts taken 10 days after onset ranging between 6000 and 9000, of which 50% to 60% were polymorphonuclear leucocytes. In only two instances were counts done at the onset of the infection and these revealed a leucocytosis of 16,000 and 18,500, respectively, with 90% to 92% polymorphonuclear leucocytes. One patient had a one plus albumin in his urine, but this was not present when the second specimen was examined 10 days later. Urinalyses on 23 patients were negative when examined 10 days after onset. Erythrocyte sedimentation rates 10 days after onset of the disease ranged from 2 to 10 ml. per hour (Cutler method). Antistreptolysin titers two weeks after the onset were 50 and 250, respectively, in the two cases who had 400,000 units SR penicillin prior to throat culture. The separate swabs of the nose, tonsils, and pharynx taken at the onset of fever in 21 cases before medication and 2 after 400,000 units SR penicillin were cultured on Klebs-Loeffler broth and blood agar media. No hemolytic streptococci were grown. The initial throat cultures of the 111 children admitted during this period showed no hemolytic Streptococcus on Klebs-Loeffler media which was the routine culture media for all admissions. Heterophile antibody agglutinations on all the 30 cases were negative when performed two weeks following admission. During this period, one child was very ill with a pneumonic process of unknown etiology. Her throat cultures on broth and blood agar were negative for hemolytic streptococci.

The over-all length of the disease averaged three days. The fever lasted from 36 hours to 4 days, the sore throat 2 to 3 days, and the rash 36 hours to 5 days. There was no desquamation. All patients were completely well subjectively, objectively, and with regard to laboratory tests 10 days after onset. There were no complications. The course of the disease was not influenced by medication. Three children were treated with acetylsalicylic acid (aspirin) as needed for fever; twenty children were treated with procaine penicillin and acetyl sulfisoxazole and seven with the tetracyclines.

Viral Studies

Throat and rectal swabs were collected from 12 cases and inoculated into HeLa-cell tissue culture tubes. No cytopathogenic changes could be demonstrated. This material is being saved for inoculation into other cell lines. Convalescent sera from two patients were used for complement fixation tests with APC (adenopharyngoconjunctival) antigen, with negative results. Convalescent sera will also be saved for further testing when measles and other antigens become available.

Differential Diagnosis

The principal difficulty in diagnosis lay in differentiating this disease from scarlet fever, German measles, Boston exanthem, erythema infectiosum, and infectious mononucleosis.

1. In scarlet fever the rash which resembles this disease begins on the neck and later appears on the trunk and in the groins. The general systemic reaction is more marked. Desquamation is the rule. In mild scarlet fever, a positive throat culture for beta hemolytic Streptococcus may be the only differentiating factor.

2. In German measles the rash first appears on the face and there are enlarged posterior occipital lymph nodes.

3. In infectious mononucleosis there is generalized lymphadenopathy; the rash which appears between the fourth and seventh days occurs in only about 10% to 20% of the cases. There are characteristic changes in the lmphocytes in the peripheral blood and a positive heterophile antibody test.

4. In measles, Koplik's spots are present and there are characteristic differences in the rash.

5. In Boston exanthem [1-2] the rash is morbilliform, and distribution over face, chest, and back is characteristic. Agents cytopathogenic for tissue cultures are isolated,

and a related neutralizing antibody response is associated.

6. In erythema infectiosum [3-6] the characteristic skin eruption bears no resemblance.

It is suggested that while this disease seems to be clinically a mild scarlet fever and is being so diagnosed in this area, the failure to culture beta hemolytic Streptococcus from the throat eliminates it, for by definition scarlet fever is "an acute infection primarily of the throat, caused by a member of the group 'A' beta hemolytic streptococcus."[6] In the disease entity which we have described, the throat cultures of all 23 cases on which they were performed have been negative for "A" beta hemolytic Streptococcus. Therefore, one must assume that this was not scarlet fever. However, it must be clearly distinguished from scarlet fever because of the hardships that would follow the erroneous diagnosis, since in the Commonwealth of Pennsylvania, as set forth in the Rules and Regulations for the Control of Communicable Diseases, "a patient with streptococcus sore throat with or without eruption is isolated for a minimum period of seven days"[7] and "no person residing on a premises on which a case of scarlet fever and/or hemolytic streptococcal sore throat exists shall engage in the sale or handling of milk or in the sale, handling or manufacture of milk products or foods, beverages, candy or tobacco except when permission is granted by the health authorities in accordance with the provisions of these regulations."[8] The child loses time at school and the adults may be cut off from necessary income.

In summary, 30 patients with sore throat, fever, and a diffuse papular, bright-red erythema resembling scarlet fever are presented. Twelve had negative throat cultures for virus on tissue culture and "A" beta hemolytic Streptococcus on blood agar and broth. An additional 11 were cultured only for "A" beta hemolytic Streptococcus on blood agar and broth and were negative. The socioeconomic importance of proper diagnosis is emphasized.

Dr. Mary N. Crawford of the Children's Hospital, Philadelphia, supervised the viral studies in this series.

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REFERENCES

1. Neva, F. A.; Feemster, R. F., and Gorbach, I. J.: Clinical and Epidemiological Features of an Unusual Epidemic Exanthem, J. A. M. A. 155: 544-549 (June 5) 1954.

2. Neva, F. A.: Second Outbreak of Boston Exanthem Disease in Pittsburgh During 1954, New England J. Med. 254:838-843 (May 3) 1956.

3. Shaw, H. L. K.: Erythema Infectiosum, Am. J. M. Sc. 129:16-22 (Jan.) 1905.

4. Herrick, T. P.: Erythema Infectiosum: A Clinical Report of 74 Cases, Am. J. Dis. Child. 31:486-495 (April) 1926.

5. Lawton, A. L., and Smith, R. E.: Erythema Infectiosum: A Clinical Study of an Epidemic in Branford, Conn., Arch. Int. Med. 47:28-41 (Jan.) 1931.

6. Nelson, W. E.: Textbook of Pediatrics, Philadelphia, W. B. Saunders Company, 1954.

7. Rules and Regulations for the Control of Communicable Disease, Commonwealth of Pennsylvania, Department of Health, December, 1952, p. 6.

8. Rules and Regulations for Control of Communicable Disease, Commonwealth of Pennsylvania, Department of Health, December, 1952, p. 6.

Gastroenteritis in Infancy

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This paper is concerned with a well-recognized disorder of infancy and childhood—especially infancy—and commonly called "gastroenteritis of infants." It is characterised chiefly by vomiting and diarrhea; fever is common, and there is a marked tendency to rapid dehydration and to dangerous alterations in the constituents of the blood. It also has epidemic qualities.

Its cause is believed to be an enteral infection (various strains of Escherichia coli, Shigella, Salmonella, etc.), though bacteriological examination of the feces may be negative. We have included a number of these "suspected" infections. We have not included in our series examples of vomiting and diarrhea due to feeding problems and parenteral infection.

All who have worked for any length of time in children's hospitals will have little doubt that gastroenteritis, in the sense that we are using the term, is, indeed, highly infectious and that it is a potentially dangerous disease. For many years it has been recognized as one of the greatest hazards to infant life, especially in communities of infants. Some forms are so infectious that they can travel round an entire infants' ward in a matter of days unless the most stringent precautions are observed. The results may be dire, especially in hospitals, where there is often the added factor of another disease to debilitate the potential victim.

It is obvious that conditions are highly favorable to the spread of enteral infection in the infants' ward, nursery, or maternity home. The "seed"—present in fecal contamination—is potentially widespread. The "soil" is fertile, since the infants, having little immunity, are highly susceptible. The "sower," whether nurse, attendant, or doctor, may inadvertently spread the infection from infant to infant, while in some districts the common housefly is still a most dangerous menace.

Nursing staffs are always liable to come under suspicion, since they handle the infants so frequently, and it seems likely that dust on floors or elsewhere and spread by shoes, brooms, or dusters often acts as the vector.

Clinicians working on this problem before 1945 must have been bewildered by the failure to discover pathogenic organisms in many severe and undoubtedly infectious cases. Shigella and Salmonella infections were, of course, well recognised, but little was known of the dangerous effects of certain strains of E. coli. Only in the last 10 years has real progress been made.

Attention must be called to the gravity of the problem as it presented in the mid-1940's. Table 1 shows the mortality rate from all forms of enteritis in patients under the age of 2 years in England and Wales during the past 10 years. Figures relating to the Administrative County of London and to the County Borough of Liverpool are also shown. It will be seen that there was a very high death rate in a densely crowded city such as Liverpool. The London figures approximate more closely those of the Country as a whole, possibly because they refer to the Administrative County of London, which includes many suburban districts where there has been little overcrowding.

It will be seen that there has been a progressive reduction in all the mortality rates

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TABLE 1.—*Deaths from Enteritis in Children Under Two Years of Age per 1000 Live Births*

	1946	1947	1948	1949	1950	1951	1952	1953	1954	Jan-June 1955
England and Wales	4.30	5.81	3.32	2.97	1.86	1.35	1.09	1.07	0.77	0.83
London Administrative County	4.30	5.06	2.61	1.87	1.10	0.82	0.86	1.26	0.45	0.65
Liverpool County Borough	21.15	21.59	13.29	7.80	3.32	2.32	2.21	1.74	0.83	0.66

during the last 10 years, and, in the case of Liverpool, this has been substantial. This improvement began before knowledge of the pathogenic coliform organisms affected clinical practice and before antibiotics were introduced. It might, of course, be that the nature of the infection changed or that the infants' resistance improved. Alternatively, it could be that cases were treated with greater medical and nursing skill or that those needing hospital treatment were diagnosed earlier and admitted to hospital more promptly. There was a decrease in the incidence of infective gastroenteritis, but the fall of the mortality rate was far greater proportionately.

cases admitted with, or developing, gastroenteritis has also shown a decrease: 561 cases in 1946 to 144 in 1954, rising to 235 in 1955 (Table 3). The largest number of deaths occurred in the younger age groups (Table 4): there were 107 out of 140 (76%) in 1946, there were 87 out of 114 (76%) in 1947, and there were 13 out of 14 (92%) in 1953, all under 6 months of age, whereas in 1954 both fatal cases were under 3 months of age. In 1955, out of seven deaths, two patients were under 3 months, two were under 6 months, and the remaining three under 9 months of age.

A certain number of infants (Table 5) were admitted in extremis and died within a

TABLE 2.—*Deaths (Under Two Years of Age) from Gastroenteritis During the Ten-Year Period, 1946-1955*

Year	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955
No. of deaths	140	114	63	32	20	15	17	14	2	7

In an attempt to elucidate these points a study has been made of the case papers of all those infants under the age of 2 years who died of gastroenteritis at the largest children's hospital in Liverpool during the past 10 years. An up-to-date survey has also been made of all cases of gastroenteritis in the same age group admitted to three Liverpool hospitals during six months of 1955.

Deaths Due to Gastroenteritis

A survey was made of deaths due to gastroenteritis in infants under 2 years of age at Alder Hey Children's Hospital, Liverpool, during the 10-year period 1946-1955. It will be seen from Table 2 that the number of deaths has fallen from 140 in 1946 to 2 in 1954 and 7 in 1955. The total number of

few hours of admission. The majority of these, as well as all those surviving longer, had intravenous fluid therapy—many on two, three, four, and five occasions. One infant had "drips" running for 24 days. The fluids used during the earlier years were varying strengths of normal saline, Hartmann's solution, plasma, and, in a few cases, whole blood. From 1949 onward, when routine serum electrolyte estimations were made Darrow's solution was given when necessary to correct potassium deficiencies. Sulfonamide drugs, penicillin, and streptomycin were frequently used, and, in later years, the newer antibiotics, oxytetracycline, chlortetracycline, chloramphenicol, and neomycin sulphate.

In patients dying after several weeks of illness there was usually an associated debili-

TABLE 3.—*Number of Cases with Gastroenteritis (Under Two Years of Age) in Alder Hey Children's Hospital During the Ten-Year Period, 1946-1955*

Year	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955
No. of cases	561	486	288	336	241	269	271	361	144	235

TABLE 4.—*Age Groups of Fatal Cases During Ten-Year Period (Alder Hey Children's Hospital)*

	Number of cases									
Age on admission	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955
Under 6 months	107	87	42	26	17	13	10	13	2	4
6–12 months	29	26	20	6	3	2	7	1	—	3
1–2 years	4	1	1	—	—	—	—	—	—	—
Total:	140	114	63	32	20	15	17	14	2	7

TABLE 5.—*Length of Stay in Hospital of 140 Fatal Cases During Ten-Year Period (Alder Hey Children's Hospital)*

	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955
Died within 24 hours	21	19	3	3	2	8	7	3	1	2
Died within 72 hours	12	6	7	1	2	—	3	—	—	1
Survived 4–7 days	33	15	11	4	1	—	—	2	—	—
Survived 8–14 days	20	24	12	5	4	2	3	2	—	3
Survived 2 weeks or longer	54	50	30	19	11	5	4	7	1	1
Total	140	114	63	32	20	15	17	14	2	7

tating illness and, in some cases, congenital deformities. These deformities included cerebral agenesis, hydrocephalus, meningocele, hydronephrosis, Mongolism, and congenital heart disease. The other commonly associated illnesses contributing to death were respiratory infections, otitis media, and mastoiditis (Table 6). Less frequently encountered were lax esophagus, diaphragmatic hernia, congenital hypertrophic pyloric stenosis, pyelitis, exfoliative dermatitis, meningococcal meningitis (one case of each), prematurity, pink disease (two cases of each), mucoviscidosis (three cases), and septicemia (four cases). The other gastrointestinal infections with fatal termination, included dysentery due to Shigella Sonnei (three cases), Salmonella typhimurium (two cases) and Salmonella Newport (two cases). Postmortem examinations were carried out in a majority of cases after 1949.

The infective nature of the disease was also investigated. Sometimes it was found that several cases were admitted from a maternity unit or residential nursery at the same time, though not all the infants infected died.

In this series pathogenic coliforms were not reported until 1949. E. coli 0.111 were found more commonly than other strains in the fatal cases. There were nine cases associated with E. coli 0.111 among the deaths in 1949, fifteen in 1950, five in 1951, six in 1952, ten in 1953, and one in 1955. On the

TABLE 6.—*Analysis of Causes of Death (Gastroenteritis Alone and Those Associated with Other Illnesses)*

	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955
Gastroenteritis alone	107	94	48	21	13	7	10	7	1	5
Gastroenteritis associated with respiratory infections	7	10	4	4	1	—	1	2	1	—
Gastroenteritis associated with otitis media or mastoiditis	22	7	10	2	—	—	—	—	—	—
Gastroenteritis associated with congenital deformities	—	—	—	—	4	2	5	4	—	1
Gastroenteritis associated with other conditions	4	3	1	5	2	6	1	1	—	1
Total	140	114	63	32	20	15	17	14	2	7

other hand, E. coli 0.55 was isolated in only two fatal cases in 1950 and three in 1952; E. coli 0.26 was found in 2 fatal cases in 1952; E. coli 0.119 was isolated in 1 case in 1953 and in 1 case in 1955.

Among those that died there was a history of previous contact with a possible source of infection in 46 out of 140 cases in 1946, in 45 out of 114 cases in 1947, and in 29 out of 63 cases in 1948. This factor would seem to be relevant and important.

Comment.—It may be permissible to give general clinical impressions, as both of us worked at this hospital throughout the 10-year period.

Technical skill (medical and nursing) would not appear to have changed significantly. In 1946, as now, intravenous transfusions were always used if there was inability to absorb fluids given by mouth, but these transfusions seemed to be of more transient value in the severe cases and frequently had to be repeated. Blood-chemistry studies were not available in earlier years, and it was not then appreciated that intracellular potassium lack was such an important factor. Antibiotics, too, were not obtainable in the earlier years, and the factor of severity of illness on admission has also to be considered. A great many were practically moribund at that time, and although intravenous fluids were usually administered within the first hour—often with greater speed—yet the child died. We believe that general practitioners were working extremely hard in the years immediately after the war and that it was a physical impossibility for them to see all the patients soon after the onset of symptoms. The hospitals were often full, and the admission of cases was sometimes delayed.

Gastroenteritis in Three Liverpool Hospitals

A survey was made of cases of gastroenteritis in children under the age of 2 years admitted to three Liverpool hospitals during the period March 1 to Aug. 31, 1955. This survey was carried out concurrently during the six-month period. The hospitals concerned were Fazakerley Hospital (Infectious Diseases), Olive Mount Children's Hospital (one isolation block), and Alder Hey Children's Hospital (two isolation wards). At the same time a control series was observed in one isolation ward at Alder Hey Children's Hospital; these infants had been admitted with various diagnoses other than gastroenteritis.

The total number of cases with gastroenteritis admitted during the six months was 466 and is shown, together with age incidence, in Table 7. The total number of control cases was 109; these, with age incidence, are also shown.

Of the gastroenteritis cases (and incidentally also of the control cases) a majority were under 6 months of age and five deaths occurred: in four cases some other condition was a contributory factor (vaccinal encephalitis, postoperative Hirschsprung's disease, staphylococcal septicemia, and hydrocephalus) and in the remaining case death from acute gastroenteritis occurred a few hours after admission.

TABLE 7.—*Number of Children Under the Age of Two Years with Clinical Gastroenteritis Admitted to Three Liverpool Hospitals During the Six Months, March 1-August 31, 1955*

Hospital	No. Admitted	No. of Deaths	Age on Admission			
			Under 1 Mo.	1 Mo. to 6 Mo.	6 Mo. to 1 Yr.	Over 1 Yr. Under 2 Yr.
Fazakerley Isolation Hospital	230	—	5	76	96	53
Olive Mount Children's Hospital (Isolation Block)	121	2	1	59	45	16
Alder Hey Children's Hospital (2 Isolation Wards)	115	3	10	55	25	25
Total	466	5	16	190	166	94
Control Group						
Alder Hey Children's Hospital (Infants' Cubicle Ward)	109	4	13	44	25	27

TABLE 8.—*Pathogenic Organisms Isolated*

Hospital	Total No. of Cases	E. Coli 0.111	E. Coli 0.119	E. Coli 0.55	E. Coli 0.26	E. Coli 0.86	E. Coli 0.128	Mixed Infections (Coliforms)	Sh. Sonnei.	Sal. Typhimu.	Mixed Infections (Sonnei/ Salmon/ Coli)	No Pathogens Isolated
Fazakerley Isolation Hospital	230	20	5	5	1	—	2	4	74	24	20	75
Olive Mount Children's Hospital (Isolation Block)	121	35	15	6	2	1	1	20	12	3	2	24
Alder Hey Children's Hospital (2 Isol. wards)	115	46	3	—	2	—	—	2	11	3	1	47
Total	466	101	23	11	5	1	3	26	97	30	23	146

In the control series there were four deaths; these were due to intracranial birth injury, encephalitis, cortical sinus thrombosis, and neonatal hepatitis.

Rectal swabs were taken on admission and feces were sent to the laboratory for culture on the following morning; these examinations were repeated at varying intervals. "Negative on discharge" signifies at least three consecutive negative swabs before discharge.

In the control group four children had positive admission swabs (two Sh. sonnei, one E. coli 0.111, and one E. coli 0.119), and all developed loose stools at an early stage of their illness. The remaining 105 infants in this group had negative admission and discharge swabs.

Of the 466 patients with clinical symptoms of gastroenteritis admitted to the three hospitals, 276 had positive admission swabs; in 21 cases a second organism later appeared. A further 44 patients had negative swabs on admission but positive swabs more than five days later. On discharge from hospital 239 were negative but 80 were still positive; one had died. In 146 cases no pathogenic organisms were isolated, although in four cases the infection was so severe that the infants succumbed.

The variety of organisms isolated will be seen in Table 8, and a clinical assessment of the severity of illness in each case appears in Table 9. "Mild" cases were those in whom there was no evidence of dehydration either on admission or at a later date. The "moderate" cases had dehydration but responded to oral fluids and antibiotics. Severe cases required intravenous fluid therapy in addition.

Although no pathogenic organisms were isolated in 146 cases, it will be seen that 110 of these came into the "mild" category.

Of the pathogenic coliforms, E. coli 0.111 was found the oftenest (101 cases), causing severe illness in 28, moderate illness in 38. In 35 cases the organism produced only mild symptoms. The majority of the mild cases infected with E. coli 0.111 occurred in the age groups over 6 months and in some of

TABLE 9.—*Clinical Assessment of Illness*

Symptoms	Total	E. Coli 0.111	E. Coli 0.119	E. Coli 0.55	E. Coli 0.26	E. Coli 0.86	E. Coli 0.128	Mixed Infections (Coliforms)	Sh. Sonnei.	Sal. Typhimu.	Mixed Infections (Sonnei/ Salmon/ Coli)	No Pathogens Isolated
Mild	300	35	11	8	2	1	2	6	89	21	15	110
Moderate	111	38	12	2	2	—	1	15	6	6	5	22
Severe	55	28	—	1	1	—	—	5	2	1	3	14
Total	466	101	23	11	5	1	3	26	97	30	23	146

Mild—No dehydration.
Moderate—Dehydrated but responded to oral fluids.
Severe—Required intravenous fluids.

those swabbed as "contact" cases, having only transient symptoms.

The second commonest strain encountered was E. coli 0.119, of which there were 23 cases, but none of these was severe. Of the other strains of E. coli there were eleven cases of 0.55, five cases of 0.26, three cases of 0.128, and one case of 0.86. Twenty-six instances occurred where more than one strain was present.

Comment.—It will be seen that the total number of cases (466) is large. The period under review was only six months, and this number does not represent the total number of infants with gastroenteritis admitted during that period to all Liverpool hospitals. The problem is indeed considerable. The pathogenic coliforms provide the greatest interest. In common with other studies, it has been found that E. coli 0.111 is the most dangerous. It was observed that there were a number of cases having two coliform strains although rarely at the same time in any one case. It is likely that this was due to cross-infection, but it is not beyond the bounds of possibility that an antibiotic suppressed one strain more readily than another in an infant who was already carrying two strains. In this respect E. coli 0.119 was found to be the commonest cross-infecting (or second) organism to appear and in several cases was very persistent.

Treatment varied slightly in the three hospitals. At Fazakerley Hospital polymyxin B sulfate or streptomycin, both given orally, were used throughout the series with excellent results. At Alder Hey and Olive Mount Children's hospitals, either oxytetracycline, chloramphenicol, or neomycin sulphate were used depending upon the sensitivity reports on the organisms. Todd and Hall [1] giving the results of that part of the Medical Research Council trial which was carried out between March, 1950, and March, 1952, noted a tendency for resistance to develop to chloramphenicol toward the end of that period, and Wheeler and Wainerman [2] found this in their series also. In the present series resistance developed to oxytetracycline in the summer of 1955, but it was then found that most strains were once again sensitive to chloramphenicol, and this drug was used with good effect. Neomycin sulphate is also proving effective at the present time.

General Comment

It is now impossible to prove bacteriological correlation between the fatal cases of enteritis in Liverpool in the 1940's and cases of enteritis found to be associated with specific E. coli types after 1950. Certain points favor the view that the cause was the same. A high degree of infectivity was noted in earlier years, despite "negative" bacteriological findings. Severe cases usually had a characteristic smell, described by Beavan [3] as a "spermatic" odor, and now known to be associated with specific E. coli types. It is also known that there were during the earlier part of the 10-year period many severe outbreaks of infantile gastroenteritis in other cities, that these also carried high mortality rates and were associated with E. coli 0.111. Bray [4] and Bray and Beaven,[5] at Uxbridge, recorded an outbreak of 50 cases in 1943 and 40 cases in 1945; E. coli 0.111 was isolated in approximately 90% and the death rate was approximately 30% in each outbreak. Giles, Sangster, and Smith [6] recorded a severe outbreak in Aberdeen in 1947; 207 infants were diagnosed as having infective enteritis and, of these, 105 (50.6%) died. E. coli 0.111 was isolated in 196 (94.7%). Taylor, Powell, and Wright [7] recorded the isolation of E. coli 0.111 from cases of infantile gastroenteritis in seven British counties during 1947; in one outbreak 20 infants in a maternity home contracted gastroenteritis and 14 died. It was generally true of all these outbreaks that they were associated with institutions of one kind or another and that cross-infection was often a very important factor. The literature was reviewed in a leading article in the *Lancet* [8] in 1952 and an estimate was then made that gastroenteritis was responsible for about a twelfth of all deaths in infancy in Great Britain as a whole—the

fraction being larger in densely populated areas.

Many authors, writing about the specific E. coli types, refer to the work of Dr. John Smith of Aberdeen and his colleagues.[6,9-13] Smith,[14] in 1955, wrote a comprehensive monograph on the whole subject. The association of certain types of E. coli with infantile diarrhea is by no means a new discovery. Smith traces early work to Bahr[15] and Bahr and Thomsen[16] whose studies date from 1908. Adam[17] concluded that a certain type of E. coli, now known to have been 0.111, was often found in cases of infantile gastroenteritis and that a second type, now known to have been 0.55, was found less frequently. Goldschmidt[18] elaborated and confirmed the association of these types of E. coli with infantile enteritis, and the observations of Cziglany,[19] following an outbreak in Budapest, added further support.

Since 1950, reports of outbreaks of infantile gastroenteritis, associated with several types of E. coli, have appeared with increasing frequency in the medical literature but, until 1953, comparatively little about these organisms was to be found in the American literature. As was stressed in a leading article in the *British Medical Journal*,[20] the problem had been investigated from different angles on the two sides of the Atlantic. In the U. S., during the 10 years from 1943, theories of a viral origin had been explored and Light and Hodes[21,22] and Gordon and his colleagues[23,24] had produced promising results. Meanwhile, in Great Britain, attention was being concentrated on those strains of E. coli now believed by many authorities to be of certain etiological importance.

It is possible that epidemics of infantile diarrhea in the U. S. were not, in the past, frequently associated with specific E. coli types. The publication of Neter, Korns, and Trussell[25] may, however, be highly significant. These authors instanced two New York hospital epidemics of enteritis among neonates in 1947 that were later shown to have been associated with E. coli 0.111; the mortality rate in one of these outbreaks was as high as 37%. Further epidemics, associated with the same organism, were described by Modica, Ferguson, and Ducey,[26] Wheeler and Wainerman,[2] Stulberg, Zuelzer, and Nolke,[27] Neter,[28] and Belnap and O'Donnell.[29] The subject was reviewed in 1954 in an editorial in the *Journal of the American Medical Association*.[30] Recently, severe outbreaks associated with E. coli 0.127 have been described by Cooper, Walters, Keller, Sutherland, and Wiseman,[31] Stulberg, Zuelzer, Nolke, and Thompson,[32] and Bernet, Graber, and Anthony.[33] In Britain this organism appears to be uncommon, but it has only been looked for since 1954. Smith,[14] commenting upon the prevalence of different types of E. coli in various parts of the world, says that the 0.111, 0.55, and 0.26 have been found in association with cases in many different countries: the 0.25 type has been found mainly in Italy, 0.44 has been reported from Finland, 0.86 from England and various parts of Europe, 0.114 from England, 0.119 from Scotland and England, 0.125, 0.126, and 0.128 from England, and 0.127 from the U. S.

A discussion on epidemic gastroenteritis would be incomplete without a brief reference to social factors. Taylor,[34] commenting upon the striking fall in the death rate from enteritis among young children in London during the past 50 years, reviews the social aspects and stresses the importance of selective rehousing among other measures.

No attempt has been made to assess such factors in the Liverpool series, although it is recognized that they are of undoubted significance.

Conclusion

The past 10 years have witnessed a sharp decline in the death rate from gastroenteritis in infants and young children. This has been very noticeable in Liverpool. A study of the fatal cases at a large Liverpool children's hospital during this period has been compared with a study of cases treated in 1955 with a death rate of less than 1%.

The following reasons are given to explain the much better prognosis in recent years:

(a) We now know much more about the changes that occur in the composition of the blood in gastroenteritis and appropriate action is taken.

(b) The 10 years have seen great advances in the bacteriological studies of E. coli strains and their relationship to gastroenteritis.

(c) Similarly these years have coincided with the discovery and application of very powerful antibiotics.

(d) There have been improvements outside the hospital sphere, including improved housing and hygiene, improved resistance of patients, a greater number of medical and ancillary personnel and a greater awareness of the special problems and dangers of the disease.

The most powerful factor of all at the present time, probably, is the effectiveness of antibiotics. It is obviously most important that the sensitivity of organisms shall be continually reassessed and the appropriate antibiotics carefully used. In this respect the clinician has to keep at least one move ahead of the organism and the investigators of antibiotics have to keep one move ahead of the clinician if these infections are to be controlled.

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Alder Hey Children's Hospital.

REFERENCES

1. Todd, R. McL., and Hall, E. G.: The Correlation of Clinical and Bacteriological Findings in Infantile Gastro Enteritis, Arch. Dis. Childhood 30:345-353 (Aug.) 1955.

2. Wheeler, W. E., and Wainerman, B.: The Treatment and Prevention of Epidemic Infantile Diarrhea Due to E. Coli 0.111 by the Use of Chloramphenicol and Neomycin, Pediatrics 14: 357-363 (Oct.) 1954.

3. Beavan, T. E. D.: Discussion on Infantile Gastroenteritis at a Meeting of the Society of Medical Officers of Health, Lancet 1:567-568 (April 29) 1944.

4. Bray, J.: Isolation of Antigenically Homogeneous Strains of Bact. Coli Neopolitanum from Summer Diarrhoea of Infants, J. Path. & Bact. 57:239-247 (April) 1945.

5. Bray, J., and Beavan, T. E. D.: Slide Agglutination of Bact. Coli var. Neapolitanum in Summer Diarrhoea, J. Path. & Bact. 60:395-401 (July) 1948.

6. Giles, C.; Sangster, G., and Smith, J.: Epidemic Gastro-Enteritis of Infants in Aberdeen During 1947, Arch. Dis. Childhood 24:45-53 (March) 1949.

7. Taylor, J.; Powell, B. W., and Wright, J.: Infantile Diarrhoea and Vomiting; Clinical and Bacteriological Investigation Brit. M. J. 2:117-125 (July 16) 1949.

8. Infantile Gastro-Enteritis, Leading Article, Lancet 2:323-325 (Aug. 16) 1952.

9. Smith, J.: The Association of Certain Types (α and β) of Bact. Coli with Infantile Gastro-Enteritis, J. Hyg. 47:221-226 (Sept.) 1949.

10. Smith, J.; Galloway, W. H., and Speirs, A. L.: Infantile Gastro-Enteritis with Special Reference to the Specific Serological Type 0 55 B5 H6 (Beta Type) of Bacterium Coli, J. Hyg. 48:472-483 (Dec.) 1950.

11. Smith, J., and Galloway, W. H.: The Sensitivity to Antibiotics of Strains of Bact. Coli Associated with Infantile Gastro-Enteritis, Arch. Dis. Childhood 28:30-35 (Feb.) 1953.

12. Smith, J.: The Association of Serological Types of Bacterium Coli with Infantile Gastro-Enteritis, J. Path. & Bact. 66:503-511 (Oct.) 1953.

13. Glover, R. E.; Lorell, R.; Smith, J., and Worrall, R. L.: Discussion: Gastro-Enteritis: The Ætiological Importance of Viruses and Bacterium Coli, Proc. Roy. Soc. Med. 47:967-970 (Nov.) 1954.

14. Smith, J.: The Aetiology of Epidemic Infantile Gastro-Enteritis, Royal College of Physicians of Edinburgh Publications, No. 5, 1955.

15. Bahr, L.: Untersuchungen über die Aetiologie der Cholera infantum: I. Bakteriologische Untersuchungen von 75 Fallen von Cholera infantum (1908 und 1909), Zentralbl. Bakt. 66:335-365, 1912.

16. Bahr, L., and Thomsen, A.: Untersuchungen über die Aetiologie der Cholera infantum: Aetiologie der Cholera infantum (1910), Zentralbl. Bakt. 66:365-386, 1912.

17. Adam, A.: Dyspepsiekoli. Sur Frage der bakteriellen Aetiologie der sogenannten alimen-

tären Intoxikation, Jahrb. Kinderh. 116:8-40 (May) 1927.

18. Goldschmidt, R.: Untersuchungen zur Ätiologie der Durchfallserkrankungen des Säuglings, Jahrb. Kinderh. 139:318-358, 1933.

19. Cziglany, F.: Dyspepsiekoli im Stuhl der gesunden und kranken Säuglinge, Arch. Kinderh. 122:147-150, 1941.

20. Epidemic Gastro-Enteritis, Annotation, Brit. M. J. 2:586 (Sept. 4) 1954.

21. Light, J. S., and Hodes, H. L.: Studies on Epidemic Diarrhea of Newborn: Isolation of Filtrable Agent Causing Diarrhea in Calves, Am. J. Pub. Health 33:1451-1454 (Dec.) 1943.

22. Light, J. S., and Hodes, H. L.: Isolation from Cases of Infantile Diarrhea of Filtrable Agent Causing Diarrhea in Calves, J. Exper. Med. 90:113-135 (Aug.) 1949.

23. Gordon, I.; Ingraham, H. S., and Korns, R. F.: Transmission of Epidemic Gastroenteritis to Human Volunteers by Oral Administration of Fecal Filtrates, J. Exper. Med. 86:409-422 (Nov.) 1947.

24. Jordan, W. S., Jr.; Gordon, I., and Dorrance, W. R.: A Study of Illness in a Group of Cleveland Families: Transmission of Acute Non-Bacterial Gastroenteritis to Volunteers: Evidence for 2 Etiologic Agents, J. Exper. Med. 98:461-475 (Nov.) 1953.

25. Neter, E.; Korns, R. F., and Trussell, R. E.: Association of Escherichia Coli Serogroup 0.111 with 2 Hospital Outbreaks of Epidemic Diarrhea of the Newborn Infant in New York State During 1947, Pediatrics 12:377-383 (Oct.) 1953.

26. Modica, R. I.; Ferguson, W. W., and Ducey, E. F.: Epidemic Infantile Diarrhea Associated with Escherichia Coli 111, B4, J. Lab. & Clin. Med. 39:122-128 (Jan.) 1952.

27. Stulberg, C. S.; Zuelzer, W. W., and Nolke, A. C.: An Epidemic of Diarrhea of the Newborn Caused by Escherichia Coli 0.111, B_4, Pediatrics 14:133-142 (Aug.) 1954.

28. Neter, E.: Escherichia Coli Diarrhea: An Outbreak Among Infants on a Surgical Ward, A. M. A. Am. J. Dis. Child. 89:564-66 (May) 1955.

29. Belnap, W. D., and O'Donnell, J. J.: Epidemic Gastroenteritis Due to Escherichia Coli 0.111, J. Pediat. 47:178-193 (Aug.) 1955.

30. Pathogenicity of Escherichia Coli, Editorial, J. A. M. A. 154:837 (March 6) 1954.

31. Cooper, M. L.; Walters, E. W.; Keller, H. M.; Sutherland, J. M., and Wiseman, H. J.: Epidemic Diarrhea Among Infants Associated with the Isolation of a New Serotype: E. Coli 0.127: B8, Pediatrics 16:215-227 (Aug.) 1955.

32. Stulberg, C. S.; Zuelzer, W. W.; Nolke, A. C., and Thompson, A. L.: Escherichia Coli 0127: B_8, a Pathogenic Strain Causing Infantile Diarrhea: I. Epidemiology and Bacteriology of a Prolonged Outbreak in a Premature Nursery, A. M. A. Am. J. Dis. Child. 90:125-134 (Aug.) 1955.

33. Bernet, C. P.; Graber, C. D., and Anthony, C. W.: Association of Escherichia Coli 0127: B8 with an Outbreak of Infantile Gastroenteritis and its Concurrent Distribution in the Pediatric Population, J. Pediat. 47:287-292 (Sept.) 1955.

34. Taylor, I.: Gastro-Enteritis in Infancy in London, Lancet 1:202-203 (Jan. 23) 1954.

Bilateral Symmetry of Skeletal Maturation in the Human Hand and Wrist

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In assessing skeletal age it is customary to examine roentgenograms of only one hand and wrist on the assumption that pronounced differences between the two sides are comparatively rare. Although homologous parts of the two sides of the skeleton may show considerable differences in development, the bulk of available evidence supports the thesis that, for all practical purposes, discrepancies between the two sides are too insignificant to constitute a source of error in the determination of skeletal status.[1-8] This inference is derived from investigations of the number and size of ossification centers in the hand and wrist, chronological order of appearance of the carpal bones and secondary epiphyses, and detailed measurements of the carpal area.

The delineation of skeletal maturation determiners of the hand and wrist, initiated by Rochlin[9] and Todd[10] and extended by Greulich and Pyle,[11] permits a more precise estimation of the developmental status of each osseous center in this skeletal area. The stages of skeletal development from birth to maturity are decipherable from the contours and changes characteristic of the articular surface of each bone, ossifying epiphysis, and subepiphyseal region. The sequences of anatomical changes in the respective centers, which comprise the maturity indicators, have been equated with chronological age. This inspectional method offers a greater degree of refinement in the assessment of skeletal age and serves as the basis for the analysis of the symmetry of bone growth incorporated in the Red-Graph method.[12] In the present study the principles of both the Todd inspectional technique and of the Red-Graph method have been applied to a quantitative evaluation and comparison of the bilateral and unilateral symmetry of the maturing human hand and wrist.

Materials and Methods

Material for analysis was obtained from roentgenograms of 450 children seen consecutively in the Nutrition Clinic of the Hillman Hospital, Birmingham, Ala. Roentgenograms of the right and left hands and wrists of each child were taken at the same visit using identical procedures for positioning, exposure, and processing. The subjects ranged in age from 1 month to 16 years 11 months. The series included 227 boys and 223 girls. The age and sex distribution is shown in

TABLE 1.—*Age and Sex Distribution of the 450 Children in the Study Group*

Chronological Age	Boys	Girls	Total
1 mo.–11 mo.	11	12	23
1 yr.–1 yr. 11 mo.	23	18	41
2 yr.–2 yr. 11 mo.	19	23	42
3 yr.–3 yr. 11 mo.	15	9	24
4 yr.–4 yr. 11 mo.	10	15	25
5 yr.–5 yr. 11 mo.	13	13	26
6 yr.–6 yr. 11 mo.	12	13	25
7 yr.–7 yr. 11 mo.	15	13	28
8 yr.–8 yr. 11 mo.	16	16	32
9 yr.–9 yr. 11 mo.	10	15	25
10 yr.–10 yr. 11 mo.	19	20	39
11 yr.–11 yr. 11 mo.	13	16	29
12 yr.–12 yr. 11 mo.	17	15	32
13 yr.–13 yr. 11 mo.	10	5	15
14 yr.–14 yr. 11 mo.	11	9	20
15 yr.–15 yr. 11 mo.	7	9	16
16 yr.–16 yr. 11 mo.	6	2	8
Total	227	223	450

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Northwestern University studies in nutrition at the Jefferson-Hillman Hospital, Birmingham, Ala. From the Department of Nutrition and Metabolism, Northwestern University. Professor of Anatomy, Temple University, School of Dentistry. (Dr. Snodgrasse); Williams-Waterman Fellow in Nutrition (Dr. Parker).

Table 1. Each was white, of British extraction, and a native of the Birmingham region.

All roentgenograms were assessed in terms of the standard for the left hand and wrist developed by Greulich and Pyle.[11] Assessments included each of the osseous centers except the pisiform and sesamoids. Values for the maturational status of each of the 28 centers, skeletal age, and degree of asymmetry were obtained for each side and the data subjected to statistical analysis.

Observations

A comparison of the incidence and direction of difference between the skeletal ages and maturational status of the 28 centers in each hand is shown in Table 2. The skeletal age of the right hand exceeded that of the left in 235 (52%) of the 450 cases. In 117 (26%) children the skeletal ages of the two hands were identical, and in 98 (22%) the skeletal age of the left hand surpassed that of the right. In the individual centers, equality in maturational status of the two hands ranged from an incidence of 22% for the radius to 42% for distal phalanx V. The incidence with which the right center was advanced over the corresponding left center ranged from 30% for the greater multangular to 57% for the radius; that wherein the left center exceeded the right extended from 18% for middle phalanx II to 43% for the lunate. The most pronounced difference in a single center occurred in the radius with the right exceeding left in 245 (57%) children, the left exceeding right in 90 (21%) and the two sides being equal in 116 (22%).

Comparison of the frequency of equality of skeletal age of the right and left hands in the 227 boys with the combined frequency of right greater than left and left greater than right for each of the 30 traits of skeletal maturation at $P=0.05$ showed that in each instance the difference was statistically significant. The upper limit of the confidence interval for the observed frequency did not attain or equal the 50% required for insignificance.[13] In the 223 girls a statistically significant difference was

TABLE 2.—*Comparison of the Maturational Status of Twenty-Eight Ossification Centers, Bone Age, and Degree of Asymmetry in the Right and Left Hand Skeletons of 450 Children*

Osseous Center	Right = Left						Right > Left						Right < Left					
	Boys		Girls		Total		Boys		Girls		Total		Boys		Girls		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Capitate	90	40	71	32	161	36	70	31	77	33	147	33	68	29	74	33	137	31
Hamate	94	42	79	36	173	39	71	32	73	33	144	32	59	26	70	31	129	29
Triquetrum	71	40	70	36	141	38	61	35	69	36	130	35	44	25	55	28	99	27
Lunate	41	26	45	26	86	26	51	33	49	29	100	31	68	41	77	45	140	43
Navicular	53	41	44	30	97	35	47	36	63	42	110	40	29	22	41	28	70	25
Gtr. multangular	36	28	43	29	79	29	41	32	41	28	82	30	50	39	62	42	112	41
Lsr. multangular	42	32	51	36	93	34	42	32	41	29	83	31	45	35	49	35	94	35
Metacarpal I	84	37	83	37	167	37	92	41	89	40	181	40	51	22	51	23	102	23
II	76	33	73	33	149	33	84	37	98	44	182	40	67	30	52	23	119	26
III	65	29	82	37	147	33	83	36	97	43	180	40	79	35	44	20	123	27
IV	69	30	74	33	143	32	85	37	87	39	172	38	73	32	62	28	135	30
V	82	32	74	33	156	35	76	33	91	41	167	37	69	30	58	26	127	28
Prox. phalanx I	71	31	67	30	138	31	81	36	81	36	162	36	75	33	75	34	150	33
II	82	36	82	37	164	36	75	33	86	39	161	36	70	31	55	25	125	28
III	70	31	91	41	161	36	90	40	81	36	171	38	67	29	51	23	118	26
IV	70	31	91	41	161	36	95	42	94	42	189	42	62	27	38	17	100	22
V	68	30	82	37	150	33	95	42	99	44	194	43	64	28	42	19	106	24
Mid. phalanx II	74	33	73	33	147	33	108	47	110	51	228	49	45	20	35	16	80	18
III	75	33	73	33	148	33	107	47	111	50	218	48	45	20	39	17	84	19
IV	81	36	69	31	150	33	101	44	108	48	209	46	45	20	46	21	91	20
V	66	29	76	34	142	31	106	47	104	47	212	47	58	23	43	19	98	21
Dist. phalanx I	74	33	93	42	167	37	92	40	73	33	165	37	61	27	57	25	118	26
II	88	39	97	43	185	41	97	43	78	35	175	39	42	18	48	22	90	20
III	87	38	96	43	183	41	87	38	74	33	161	36	53	23	53	24	106	24
IV	94	41	88	39	182	40	77	34	80	36	157	34	56	25	55	25	111	25
V	92	40	96	43	188	42	84	37	80	36	164	36	51	22	47	21	98	22
Radius	53	24	42	20	95	22	116	53	129	61	245	57	59	23	40	19	99	21
Ulna	39	31	58	45	97	38	60	48	53	41	113	44	27	21	17	13	44	17
Range	42	18	40	18	82	18	88	39	94	42	182	40	97	43	89	40	186	41
Skeletal age	51	22	66	30	117	26	124	55	111	50	235	52	52	23	46	20	98	22

TABLE 3.—*Comparison of the Incidence and Degree of Inequality of Maturational Status in Right and Left Hand Skeleton in 450 Children*

Osseous Center	Right>Left															Right<Left													
	1-3 Mo.			4-6 Mo.			7-9 Mo.			10-12 Mo.			>12 Mo.			1-3 Mo.			4-6 Mo.			7-9 Mo.			10-12 Mo.			>12 Mo.		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
Capitate	41	41	82	20	28	48	5	4	9	4	2	6	0	2	2	33	17	50	12	24	36	8	5	13	7	6	13	3	2	5
Hamate	44	37	81	18	29	47	6	4	10	3	1	4	0	2	2	28	41	69	21	18	39	6	5	11	4	5	9	0	1	1
Triquetrum	24	33	57	25	28	53	6	2	8	5	2	7	1	4	5	20	33	53	16	12	28	5	4	9	1	5	6	2	1	3
Lunate	16	23	39	22	14	36	6	6	12	5	2	7	2	4	6	22	31	53	15	24	39	10	12	22	12	5	17	4	5	9
Navicular	13	28	41	21	25	46	9	4	13	3	6	9	1	0	1	12	26	38	9	7	16	2	0	2	5	3	8	1	5	6
Gtr. Multangular	17	19	36	9	14	23	8	3	11	5	3	8	2	2	4	14	22	36	16	20	36	13	6	19	5	8	13	2	6	8
Lsr. Multangular	16	13	29	14	21	35	7	2	9	5	2	7	0	3	3	11	20	31	17	13	30	9	6	15	6	6	12	2	4	6
Metacarpal I	45	60	105	31	22	53	11	3	14	3	2	5	2	2	4	32	35	67	9	10	19	7	3	10	3	1	4	0	2	2
II	51	63	114	19	23	42	9	7	16	3	4	7	2	1	3	37	35	72	17	11	28	11	4	15	1	1	2	1	1	2
III	54	61	115	19	21	40	9	6	15	0	5	5	1	4	5	42	26	68	24	12	36	5	3	8	5	2	7	3	1	4
IV	60	52	112	12	22	34	7	6	13	6	3	9	0	4	4	40	37	77	21	17	38	7	6	13	5	1	6	0	1	1
V	44	56	110	19	25	44	7	7	14	5	2	7	1	1	2	39	37	76	22	17	39	6	2	8	2	1	3	0	1	1
Prox. Phalanx I	45	51	96	21	19	40	6	6	12	8	4	12	1	1	2	30	38	68	22	21	43	10	9	19	9	6	15	4	1	5
II	42	50	92	15	22	37	12	7	19	6	5	11	0	2	2	47	35	82	10	13	23	9	3	12	3	4	7	1	0	1
III	48	46	94	28	22	50	8	6	14	5	6	11	1	1	2	43	29	72	16	17	33	4	2	6	4	2	6	0	1	1
IV	51	48	99	25	33	58	13	7	20	6	5	11	0	1	1	37	25	62	13	10	23	8	3	11	3	0	3	1	0	1
V	57	57	114	22	29	51	9	6	15	6	6	12	1	1	2	39	25	64	18	15	33	2	1	3	5	1	6	0	0	0
Mid. Phalanx II	58	71	129	29	27	56	14	14	28	5	2	7	2	1	3	28	22	50	9	8	17	6	2	8	2	3	5	0	0	0
III	56	64	120	30	31	61	14	12	26	5	3	8	2	1	3	23	21	44	15	15	30	5	0	5	1	3	4	1	0	1
IV	50	63	113	29	31	50	17	11	28	5	2	7	0	1	1	20	27	47	15	14	29	8	3	11	1	2	3	1	0	1
V	41	65	106	39	25	64	13	13	26	11	3	14	4	1	5	30	17	47	12	17	29	6	5	11	3	3	6	2	1	3
Dist. Phalanx I	49	40	89	22	20	42	9	6	15	6	4	10	6	3	9	27	26	53	17	12	29	9	10	19	7	9	16	1	0	1
II	40	47	87	38	21	59	11	6	17	4	3	7	4	1	5	23	28	51	11	17	28	6	2	8	2	1	3	0	1	1
III	47	45	92	20	21	41	14	6	20	5	1	6	1	1	2	30	34	64	12	15	27	7	3	10	4	1	5	0	0	0
IV	43	45	88	16	24	40	11	7	18	6	2	8	1	2	3	25	38	63	20	12	32	5	2	7	6	3	9	0	0	0
V	48	45	93	22	25	47	6	6	12	7	2	9	1	2	3	23	24	47	18	19	37	4	4	8	6	0	6	0	0	0
Radius	42	53	95	38	35	73	12	20	32	19	14	33	5	7	12	27	22	49	18	11	29	2	6	8	2	1	3	1	0	1
Ulna	18	24	42	15	11	26	12	4	16	7	9	16	8	5	13	9	8	17	10	5	15	4	4	8	3	0	3	1	0	1
Range	45	48	93	22	26	48	9	10	19	8	3	11	4	7	11	45	42	87	26	30	56	11	8	19	8	4	12	7	5	12
Skeletal Age	106	97	203	17	10	27	1	2	3	0	1	1	0	1	1	46	42	88	6	4	10	0	0	0	0	0	0	0	0	0

obtained for all except the ulna. Considering the advancement of right and left hand relative to each other, the differences in frequency for the boys was significantly greater (P=0.05) for the right hand for each of 15 centers † and skeletal age; the upper level of the confidence interval for the observed frequency did not attain or equal 50%. In the girls significant values were obtained for 17 centers ‡ and skeletal age.

As shown in Table 3, in 291 (87%) of the 333 cases of inequality of skeletal age between the two sides, the difference was between one and three months. In 37 (11.5%) instances the difference was between four and six months, and in only 5 (1.5%) children did the discrepancy exceed six months. For the specific osseous centers, deviations greater than six months were encountered most frequently in the lunate, metacarpal II, proximal phalanx I, middle phlanges, distal phalanx I, and radius. Differences greater than 12 months were noted most commonly in the carpal area. The presence of a carpal center on one side and its absence on the other accounted for 17 of the discrepancies in this series distributed as follows: triquetrum 2 (1 right, 1 left), lunate 3 (3 right), navicular 4 (4 left), greater multangular 4 (2 right, 2 left) and lesser multangular 4 (1 right, 3 left).

In Table 4 the over-all maturational status of the right and left hand skeletons of the 450 children have been grouped according to speed of skeletal development. In 88 (19%) of the cases skeletal age exceeded chronological age on both sides, in 22 (5%) skeletal age equaled chronological age on one or both sides and in 344 (76%) chronological age was greater than skeletal age on both sides. In each of the advanced, par, and retarded groups the commonest relationship was a skeletal age of the right hand in excess of the left. The ratios of the number in which right exceeded left, right equaled left, and left exceeded right were of the same order of magnitude for both the advanced and retarded groups. As a group the children progressing at par contained a higher percentage of cases in which right equaled left and a lower percentage in which left exceeded right than in the advanced and retarded groups.

The mean difference between skeletal age and chronological age for the right and left hands of the 450 children throughout the age range included in this study is presented in Table 5. The values represent the summation of both positive and negative differences regardless of sign. Only in age group 1 month through 11 months did the mean difference fall below 3 months. Beginning with age group 2 years through 2 years 11 months, the mean deviation exceeded 6 months in every instance. The peak mean difference of slightly more than 16 months was obtained for age group 6 years through 6 years 11 months.

Table 6 contains a comparison of the incidence with which the difference between the skeletal ages of the two hands surpassed, equaled, or was exceeded by the difference between the most advanced and least advanced center in each hand. In 440 (98%)

† Triquetrum, navicular, metacarpal I, proximal phalanges IV, V, middle phalanges II, III, IV, V, distal phalanges I, II, III, V, radius, ulna, and skeletal age.

‡ Navicular, metacarpals I, III, V, proximal phalanges II, III, IV, V, middle phalanges II, III, IV, V, distal phalanges II, IV, V, radius, ulna, and skeletal age.

TABLE 4.—*Comparison of Maturational Status of Right and Left Hand Skeleton with Speed of Skeletal Development in 450 Children*

Skeletal Development	Right = Left						Right > Left						Right < Left					
	Boys		Girls		Total		Boys		Girls		Total		Boys		Girls		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Advanced	8	24	12	24	20	24	18	53	30	60	48	57	8	24	8	16	16	18
Par	4	44	5	38	9	41	3	33	7	54	10	45	2	22	1	8	3	14
Retarded	39	21	49	31	88	25	103	56	74	46	177	51	42	23	37	23	79	23

TABLE 5.—*Mean Differences Between Skeletal Age and Chronological Age in Right and Left Hand of 450 Children*

Chronological Age	Mean Difference (Months)					
	Right Hand			Left Hand		
	Boys	Girls	Total	Boys	Girls	Total
1 mo.-11 mo.	1.55	1.17	1.39	1.73	1.33	1.52
1 yr.-1 yr. 11 mo.	3.22	4.78	3.90	3.43	4.22	3.78
2 yr.-2 yr. 11 mo.	6.68	6.09	6.36	6.76	6.91	6.86
3 yr.-3 yr. 11 mo.	11.67	11.56	11.25	11.80	10.89	11.46
4 yr.-4 yr. 11 mo.	11.20	9.87	10.40	10.80	9.93	10.28
5 yr.-5 yr. 11 mo.	13.69	13.31	13.50	15.15	13.08	14.12
6 yr.-6 yr. 11 mo.	16.25	16.85	16.18	15.92	17.23	16.19
7 yr.-7 yr. 11 mo.	12.73	13.15	12.93	13.45	13.38	13.43
8 yr.-8 yr. 11 mo.	9.06	8.69	8.88	10.75	9.13	9.94
9 yr.-9 yr. 11 mo.	11.80	14.27	13.28	12.60	15.00	14.04
10 yr.-10 yr. 11 mo.	10.05	12.95	11.54	10.84	13.85	12.38
11 yr.-11 yr. 11 mo.	6.15	9.06	7.76	8.08	9.75	9.00
12 yr.-12 yr. 11 mo.	9.94	10.27	10.09	10.83	10.60	10.72
13 yr.-13 yr. 11 mo.	8.20	11.40	9.93	8.20	13.20	9.87
14 yr.-14 yr. 11 mo.	8.18	6.67	7.50	7.55	6.22	6.95
15 yr.-15 yr. 11 mo.	12.71	13.71	13.13	13.00	16.11	14.75
16 yr.-16 yr. 11 mo.	10.83	7.50	10.00	10.67	9.50	10.37

children the range in both the right and left hand surpassed the difference in skeletal age between the two hands. In only 4 (1%) children, each of whom was under one year of age, did the difference between hands exceed the range within the right and left hand. The greatest difference between skeletal ages noted in this series was 1 year 5 months in an 11-year-1-month-old girl; the greatest range for the right hand was 4 years 11 months in a 6-year-10-month-old boy and for the left hand, 4 years 8 months in a 12-year-9-month-old boy.

tion of the two hands are so minor as to be negligible in the evaluation of skeletal status from roentgenograms.

Using differences in the number of osseous centers as a criterion of skeletal maturation, Torgersen [5] reported that in 404 children below 9 years of age, the right hand was more advanced in 60 and the left in 95. The inequality was interpreted as attributable to a richer nerve supply on the right side. In 25 cases in which an epiphyseal center was present in only one hand, Flecker [6] found 16 in the right side and 9 in the left.

TABLE 6.—*Comparison of Difference in Skeletal Maturity Between Right and Left Hands and Range of Maturity Within Each Hand Skeleton of 450 Children*

	Difference Between Hands >Right Range	Difference Between Hands <Right Range	Difference Between Hands =Right Range	Difference Between Hands >Left Range	Difference Between Hands <Left Range	Difference Between Hands =Left Range
Boys	0	227	0	0	226	1
Girls	4	213	6	4	214	5
Total	4	440	6	4	440	6

Comment

In his Atlas of Skeletal Maturation (Hand), Todd [10] states that "Assessors of greatly unequal experience readily assess the maturity of skeletal roentgenograms within a six-month divergence." Application of a tolerance of 6 months to the data in this series shows only 5 of 450 children with a dissimilarity between skeletal ages of the two hands greater than 6 months. The present findings thus confirm the contention that divergencies in the over-all skeletal matura-

In Elgenmark's [7] series of 59 children, 4 had ossific centers in the right and 7 in the left hand which were absent in the opposite member. Caffey [14] noted that as a rule, the secondary epiphyseal centers of the tubular bones exhibit a more uniform development than do the primary centers of the small round bones of the wrist. A greater uniformity in development of the phalanges and metacarpals in contrast to the carpals was found in this study. The present data, derived from a method in which presence of an ossification center is but one of several

factors employed in the analysis of skeletal maturation, show that the right hand was more advanced in 235 cases and the left in 98. These findings do not support Torgersen's [5] claim that maturation proceeds more slowly in the right hand, particularly on the radial side and in the thumb.

Pryor [8] holds that because of numerous ossification centers there are many opportunities for asymmetry in each hand, whereas bilateral symmetry is nearly perfect. In the present study perfect bilateral symmetry in the form of identity of skeletal age in the two sides was noted in but 117 (26%) of the 450 children. The degree and incidence of asymmetry within either hand greatly exceeds the difference in skeletal age between the two sides regardless of speed of skeletal development, thereby emphasizing the value of the Red-Graph method [12] in elucidating this feature of skeletal growth in a given hand.

Summary and Conclusions

The symmetry of skeletal development in the right and left hands of 450 children ranging in age from 1 month to 17 years was determined from roentgenograms by the Todd inspectional technique. The data showed the following:

1. Skeletal age of the right hand respectively surpassed, equaled, and was exceeded by that of the left hand in 235 (52%), 117 (26%), and 98 (22%) of the children.

2. The difference between skeletal ages of the two hands exceeded three months in 42 (13%) children and six months in only 5 (1.5%) children.

3. The differences between the skeletal maturities of the two hands was not related to the speed of skeletal development.

4. The mean difference between skeletal age and chronological age in each hand was greater than 6 months throughout the age range of 2 years to 17 years.

5. The amount of asymmetry in skeletal maturation within each hand was substantially greater than between the two hands in 440 (98%) of the 450 children.

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REFERENCES

1. Long, E., and Caldwell, E. W.: Some Investigations Concerning the Relation Between Carpal Ossification and Physical and Mental Development. Am. J. Dis. Child. 1:113, 1911.

2. Stettner, E.: Über die Beziehungen der Ossifikation des Handskellets zu Alter und Längenwachstum bei gesunden und kranken Kindern von der Geburt bis zur Pubertät, Arch. Kinderh. 68: 342, 1921.

3. Baldwin, B. T.; Busby, L. M., and Garside, H. V.: Anatomic Growth of Children: A Study of Some Bones of the Hand, Wrist, and Lower Forearm by Means of Roentgenograms, (Studies in Child Welfare), Iowa City, Iowa, University of Iowa, 1928, Vol. 4, No. 1.

4. Sawtell, R. O.: Ossification and Growth of Children from One to Eight Years of Age, Am. J. Dis. Child. 37:61, 1929.

5. Torgersen, J.: Asymmetry and Skeletal Maturation, Acta radiol. 36:521, 1951.

6. Flecker, H.: Roentgenographic Observations of the Times of Appearance of Epiphyses and Their Fusion with the Diaphyses, J. Anat. 67: 118, 1932.

7. Elgenmark, O.: The Normal Development of the Ossific Centres During Infancy and Childhood: Clinical, Roentgenologic, and Statistical Study, Acta pædiat. 33:1-79 (Suppl. 1), 1946.

8. Pryor, J. W.: Bilateral Symmetry as Seen in Ossification, Am. J. Anat. 58:87, 1936.

9. Rochlin, D. G.: Röntgenosteologie und Röntgenanthropologie, Mockba, Biomedgiz, 1936.

10. Todd, T. W.: Atlas of Skeletal Maturation (Hand), St. Louis, C. V. Mosby Company, 1937.

11. Greulich, W. W., and Pyle, S. I.: Radiographic Atlas of Skeletal Development of the Hand and Wrist: Based on the Brush Foundation Study of Human Growth and Development Initiated by T. Wingate Todd, Stanford, Calif., Stanford University Press, 1950.

12. Pyle, S. I.; Mann, A. W.; Dreizen, S.; Kelley, H. J.; Macy, I. G., and Spies, T. D.: A Substitute for Skeletal Age (Todd) for Clinical Use: The Red Graph Method, J. Pediat. 32: 125, 1948.

13. Mainland, D.: Elementary Medical Statistics: The Principles of Quantitative Medicine, Philadelphia, W. B. Saunders Company, 1952.

14. Caffey, J.: Pediatric X-Ray Diagnosis: A Textbook for Students and Practitioners of Pediatrics, Surgery & Radiology, Ed. 2, Chicago, The Year Book Publishers, Inc., 1950.

The Aplastic Crisis of Sickle-Cell Disease

Occurrence in Several Members of Families Within a Short Period of Time

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The "aplastic crisis" of congenital spherocytic anemia is a well-documented syndrome.[1,2] It is known that these erythroblastopenic states may occur in several members of a family within a short period of time. Recently these crises have been also described in sickle-cell anemia.[3,4] The purpose of this article is to report on members of two families with sickle-cell anemia in which aplastic crises developed within a short period of time.

Report of Cases

Family A

CASE 1A.—This 5-year-old Negro boy was admitted to the hospital on Nov. 28, 1955. He had been known to have sickle-cell anemia since the age of 5 months. In November and December, 1954, he had had two attacks of cerebral thrombosis leaving him with aphasia and inability to properly handle his oral secretion and a paresis of his left upper extremity. One day prior to admission he was noted to be pale and weak.

On physical examination his temperature was 101.8 F, pulse rate 100, and respirations 30 per minute. He appeared pale and apathetic, but no jaundice was noted. There was mild pharyngeal and tonsillar hyperemia. His anterior cervical lymph nodes were somewhat enlarged but nontender. The heart appeared somewhat enlarged to percussion. There was a Grade IV systolic murmur heard all over the precordium. His lungs were clear. His liver was palpable 6 cm. below the right costal margin, and the spleen was palpable 2.0 cm. below the left costal margin. The abdomen was soft and nontender.

Neurologic examination of the patient revealed a left facial weakness with drooling and a slight paresis of the left arm with somewhat hyperactive reflexes on this side. No pathological reflexes were elicited.

Laboratory Data.—Urine: 2+ albumin and trace of acetone, numerous yeast and pus cells. This was later repeated and found to be negative. No urine culture was obtained. Blood: hemoglobin, 3.4 gm. per 100 cc.; red blood cells, 910,000; white blood cells, 5900. Films showed no polychromatic erythrocytes but many target cells and sickle forms. Differential count: Neutrophils, segmented 41%, basophilic granulocytes 1%, lymphocytes 35%, monocytes 9%, and plasmacytes 14%. There were no nucleated red cells present. Platelets, 828,000 per cubic millimeter. Reticulocytes, 0.0%. Direct and indirect Coombs' tests negative. Van den Bergh: total bilirubin, 2.2 mg. per 100 cc.; direct, 0.3 mg. per 100 cc., and indirect, 1.9 mg. per 100 cc. Cephalin flocculation, 1+ at 48 hours. Chest x-ray was negative.

Course.—Because of the absence of reticulocytes, an iliac bone marrow test was performed on admission (Table). The marrow was cellular and megakaryocytes were normal in number and appearance. There was a marked reduction in erythroid elements. A few young pronormoblasts were present, but only a rare mature erythroid cell could be found. Those that were seen had basophilic stippling in their cytoplasm. The leukocytic series was normal except for a moderate increase in lymphocytes and slight increase in plasma cells.

Because of the severe anemia the patient was given 150 cc. of whole blood on the evening of admission and 200 cc. of blood on the following day. The blood transfusions increased the level of hemoglobin to 6.5 gm. per 100 cc. and the red blood count to 1,910,000. A marked improvement in his condition was noted. On admission he had been started on 300,000 units of procaine penicillin daily. By the third day his temperature became normal.

Hematologically, his reticulocyte count stayed less than 1% until Dec. 4, 1955, when 1.2% were present. Three days later the number of reticulated red cells amounted to 12.5%. The bone marrow examination showed a complete reversal of the previous findings, with marked erythroid hy-

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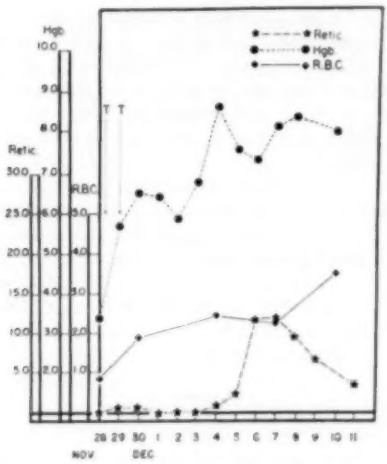

Fig. 1.—Hematologic values in Case 1A.

perplasia, the polychromatic normoblasts being the predominant cell. On Dec. 8, 1955, the patient's hemoglobin was 8.4 gm. per 100 cc., with 8900 leukocytes. There were 4 nucleated red blood cells per 100 white cells on the smear. The patient's hemoglobin remained at this level until discharge (Fig. 1).

He was seen three and one-half months after discharge, having been asymptomatic since that time. His liver was 4.0 cm. below the right costal margin, and the spleen was not palpable. A hematologic examination showed a hemoglobin level of 7.2 gm. per 100 cc. and 2,460,000 red blood cells with a reticulocyte count of 24.6%. At this time his total bilirubin was 3.8 mg. per 100 cc. with a direct reacting bilirubin of 0.2 mg. per 100 cc.

Case 2A.—This 7-year-old Negro boy, the sibling of the case described previously, was admitted to the hospital on Dec. 7, 1955. He was known to have had sickle-cell anemia since 9 months of age. Four days prior to this admission he was noted to be in a weakened condition and complained of headache and abdominal pain.

Physical examination revealed a well-developed and well-nourished Negro boy. His temperature was 101 F, pulse rate 124, and respirations 18 per minute. There was marked pallor of the mucous membrane; no jaundice was noted. A moderately loud apical systolic murmur was audible over the entire precordium with a palpable thrill over the same area. The liver extended 8 cm. below the right costal margin, but no spleen was palpable. The remainder of the physical examination was negative.

Laboratory Data.—Urine: faint trace of albumin and 6-8 white blood cells. Blood: hemoglobin on the night of admission 3.9 gm. per 100 cc. The following day after a blood transfusion a complete blood count showed the following: hemoglobin, 5.4 gm. per 100 cc.; red blood cells, 2,040,000; white blood cells, 11,400. Smear: many target cells and sickle forms and no polychromatophilic erythrocytes were seen. No nucleated red cells were present. The platelets appeared normal. There was a monocytosis and an increase in plasmacytes. Differential: neutrophils, segmented, 18%; eosinophilic granulocytes, 5%; basophilic granulocytes, 1%; adult lymphocytes, 46%, mono-

Table 1.—*Bone Marrow Studies: Differential Count of Nucleated Red Cells*

Case	Date	Myeloid: Erythroid Ratio	Pronormoblasts (per Cent)	Basophilic Normoblasts (per Cent)	Polychromatic and Orthochromatic Normoblasts (per Cent)
1 A	11/28/55	40:1	3.34	0.0	0.33
	12/2/55	3.3:1	10.0	18.7	0.0
	12/5/55	1.7:1	0.25	1.0	46.0
2 A	12/8/55	50:1	1.93	0.0	0.0
	12/11/55	1.7:1	5.66	25.0	5.0
	12/20/55	1.1:1	2.0	14.7	27.0
1 B (First adm.)	11/24/55	46:1	2.7	0.5	0.75
	11/28/55	1:3	0.25	3.7	68.0
2 B	12/7/55	1:2.5	0.32	16.1	49.4
	12/10/55	1:1	0.6	1.8	38.2
	12/20/55	1:1.2	1.33	6.65	54.0
3 B	12/7/55	3.7:1	0.0	0.0	17.0
	12/9/55	5:1	0.0	0.0	13.75
	12/11/55	9:1	0.33	0.66	6.7
	12/13/55	12:1	2.0	0.33	6.3
	12/15/55	2.3:1	5.3	30.6	3.0
	12/20/55	1.5:1	1.0	2.0	31.6
1 B (Second adm.)	1/9/56	6.4:1	1.33	4.33	10.0
	1/11/56	5.6:1	0.33	4.3	6.9
	1/13/56	2.9:1	2.3	11.7	23.6
	1/16/56	2.0:1	1.33	8.35	33.6
	1/28/56	1:1.1	0.65	3.9	45.0

cytes, 10%, and plasmacytes, 20%. Reticulocyte count was 0.1%. The platelet count was 466,500 on Dec. 12, two days after admission. Direct and indirect Coombs' tests were negative. Van den Bergh: total bilirubin, 0.3 mg. per 100 cc.; direct, 0.2, and indirect, 0.1 mg. per 100 cc.

X-ray examination of the chest revealed considerable enlargement of the heart. The lung fields were clear. Roentgenogram of the long bones revealed no evidence of any abnormality. The patch test was negative.

Course.—An iliac crest bone marrow examination done the day following admission (Table) was normocellular but contained few erythroid elements, only a few pronormoblasts being present. The megakaryocytes and leukocytic elements were normal with the exception of some increase in lymphocytes.

Because of his tonsillitis the patient was placed on oral tetracycline. Within 24 hours his fever had subsided. On the night of admission 200 cc. of whole blood was given. This brought his hemoglobin level up to 5.4 gm. per 100 cc. by the following day, but two days later it dropped to 4.5 gm. per 100 cc., with a red blood cell count of 1,800,000. He was again given 200 cc. of whole blood. Reticulocytes were not present on that day, but a bone marrow examination revealed

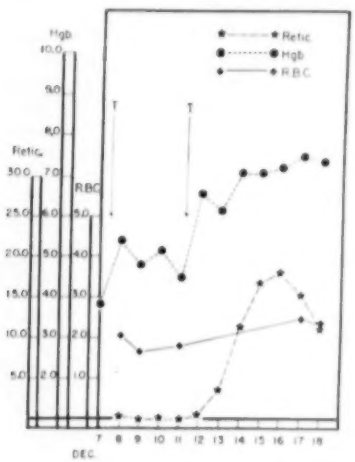

Fig. 2.—Hematologic values in Case 2A.

erythrocytic hyperplasia with many mature normoblasts. Two days later (Dec. 13, 1955) 4.1% reticulocytes were present in the peripheral blood, and the leukocyte count was 38,000, with 47 nucleated red cells per 100 white cells. Twenty three per cent monocytes were also present. The reticulocyte count continued to rise to a peak count of 18.1%, and the hemoglobin, which was 6.6 gm. per 100 cc. the day after the second transfusion, rose to 7.4 gm. per 100 cc. with the reticulocytosis. The white blood count on Dec. 18, 1955, after the peak of reticulocytosis, was 17,000 with 21 nucleated red cells per 100 white blood cells, and the monocyte count had dropped to 10%. He was discharged 15 days after admission in good condition (Fig. 2).

He was seen three months after his illness, and he had been asymptomatic since he left the hospital. His liver was palpable 5.0 cm. below the right costal margin, but no spleen was felt. His red cell count at this time was 2,570,000, with 7.0 gm. per 100 cc. of hemoglobin and 18.5% reticulocytes. His total bilirubin was 3.8 mg. per 100 cc. with 0.2 mg. per 100 cc. direct.

Family B

Case 1B (First Admission).—This 8-year-old Negro boy was admitted Nov. 24, 1955. He had been diagnosed as having sickle-cell anemia at 4 years of age at another hospital. Over the past three to four years this child had had intermittent episodes of jaundice and abdominal pain accompanied by weakness and anorexia. These had become progressively worse.

Four days prior to admission the patient developed emesis which subsided spontaneously. On the day of admission mild chest and abdominal pain occurred with weakness and anorexia. Family history revealed that the mother of this patient had received treatment for syphilis in 1941, prior to the birth of this child.

Physical examination revealed a fairly well-developed, well-nourished, and pale Negro boy not in acute distress. The temperature was 99.6 F rectally, pulse rate 130, respirations 32 per minute, and blood pressure 110/80. The patient's sclerae were muddy in appearance, but no definite jaundice was seen. Examination of the ears, nose, and throat was not remarkable. The lungs were clear to percussion and auscultation. There was a Grade II systolic murmur over the apical and aortic area of the heart. The liver was palpable 4 cm. below the right costal margin, and the spleen could be felt 1.0 cm. below the left costal margin. The remainder of the physical examination was negative.

Laboratory Data.—Urinalysis: negative except for an occasional white blood cell. Blood: hemoglobin, 4.5 gm. per 100 cc.; red blood cells, 1,670,000; white blood cells, 9200. Smear: no polychromasia of red cells or nucleated red cells was seen, and many sickle forms and target cells were present. Platelets appeared somewhat increased and were well clumped. No reticulocytes were present in the reticulocyte preparation. Differentiatial count: neutrophils, segmented, 46%; monocytes, 12%; lymphocytes, 36%, and plasma-

cytes, 5%. A sickling preparation done the following day after transfusion showed 30% holly-leaf sickling. Direct and indirect Coombs' tests were negative. Blood sugar, 100 mg. per 100 cc.; total serum protein, 8.3 gm. per 100 cc., with a normal A/G ratio. Van den Bergh reaction showed no direct bilirubin and a 1.0 mg. per 100 cc. total bilirubin. Icterus index, 13.5 units. His VDRL qualitative was 4+; VDRL quantitative positive 1:4, and Treponema pallidum immobilization test was positive. Standard Kahn and Kolmer tests were negative.

The patch test was negative. A chest x-ray taken the day after admission showed generalized cardiac enlargement and some suggestion of pulmonary congestion.

Course.—Because of the absence of reticulocytes in his peripheral blood an iliac bone marrow examination was performed (Table). The general cellularity appeared slightly decreased. There was a hypoplasia of erythroid elements with only a few pronormoblasts and normoblasts present. There was no abnormality of the megakaryocytes or leukocytic elements.

Because of the aplastic picture and his general condition, a transfusion of 200 cc. of whole blood was given that night and 300 cc. of blood on the following day. His hemoglobin level on the day after the second transfusion was 5.5 gm. per 100 cc. He remained reticulocytopenic until the fifth day of hospitalization, when 3.3% reticulocytes were counted. On this day a bone marrow examination was performed which showed a reversal of the previous picture. The cellularity was mildly increased, and marked erythroid hyperplasia was present, with many basophilic and polychromatic normoblasts. The reticulocyte count gradually rose to 27.6% on the eighth hospital day (Dec. 2, 1955). The patient maintained an elevated reticulocyte count (10%) for the remainder of this admission. On Nov. 30, 1955, during the period of increasing reticulocytosis a leukocyte count was found to be 22,350, with 60 nucleated red blood cells per 100 white blood cells. The patient improved very rapidly within the first two days of his admission and remained asymptomatic for the remainder of his hospital stay (Fig. 3).

On Dec. 7, 1955, two other members of the family of the previously described patient were admitted to the hospital. They are described below:

CASE 2B.—This 6-year-old Negro girl was apparently in good health until one week prior to admission, when she had an onset of lumbar and lower abdominal pain, anorexia, and vomiting. Her past history revealed that at 3 years of age

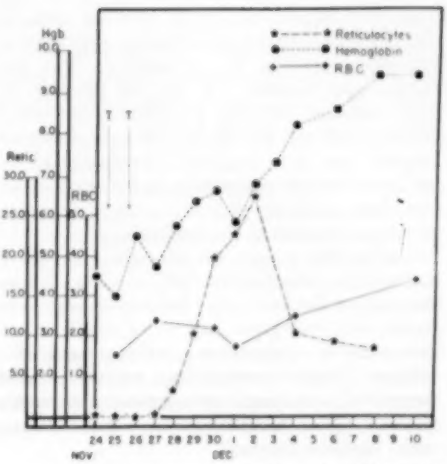

Fig. 3.—Hematologic values in Case 1B (first admission).

she was hospitalized at another hospital for back pain. Polio was suspected, and a spinal tap was done. This gave negative results, and the patient was discharged without a definite diagnosis. According to the parents the patient was not known to have sickle-cell anemia.

Physical examination revealed a well-developed and well-nourished Negro girl who was very pale, but without jaundice. Temperature, 98.4 F; pulse rate 100 per minute. There was moderate tonsillar hypertrophy without hyperemia. Examination of the nose and ears was negative. The lungs were clear to percussion and auscultation. There was a Grade II systolic murmur in the pulmonic area, but no cardiac enlargement was present. Examination of the abdomen revealed the liver palpable 2 cm. below the right costal margin and spleen 4.0 cm. below the left costal margin. There was some bilateral lower abdominal tenderness without guarding or rebound. No other abnormalities were found on physical examination.

Laboratory Data.—Urine: albumin 1+, and 8-10 white blood cells were seen. No growth on urine culture. VDRL, Kahn, Kolmer, and Treponema pallidum immobilization tests were all negative. Blood: hemoglobin, 3.8 gm. per 100 cc.; red blood cells, 1,290,000; white blood cells, 50,950. Platelets two days after admission were 431,300. Smear: many target cells and sickle forms were seen and there was a mild increase in polychromasia; there were 200 nucleated red blood cells per 100 white blood cells. Platelets appeared normal in number and were well clumped. Differential count: neutrophils: segmented, 54%; nonsegmented, 10%; metamyelocytes, 4%; eosinophilic granulocytes, 1%; basophilic granulocytes, 7%; lymphocytes, 14%; monocytes, 10%, and plasma-

cytes, 1%. Reticulocytes, 2.5%. Sickling preparation with metabisulphite solution was positive 10%-20% after the first transfusion. Van den Bergh: total bilirubin, 0.4 mg. per 100 cc.; indirect bilirubin, 0.35 mg. per 100 cc., and direct bilirubin, 0.05 mg. per 100 cc. Direct and indirect Coombs' tests were negative. Roentgenogram of the chest showed enlargement of the heart in the transverse diameter. X-ray examination of the long bones showed no abnormalities.

Course.—The patient did not appear in severe distress on admission but did complain of abdominal and low back pain. Because of her severe anemia she was given 200 cc. of whole blood. Bone marrow examination on the night of admission (Table) revealed an extreme erythroid hyperplasia with many polychromatic normoblasts present. The megakaryocytic and leukocytic series appeared normal.

The reticulocyte count rose gradually over four days to 21.3% and then leveled off at 10%. The hemoglobin level on the day following transfusion was 5.8 gm. per 100 cc. but continued to climb, reaching 8.5 gm. per 100 cc. by the 11th hospital day. The bone marrow, which had been in a hyperplastic phase on admission, returned to a

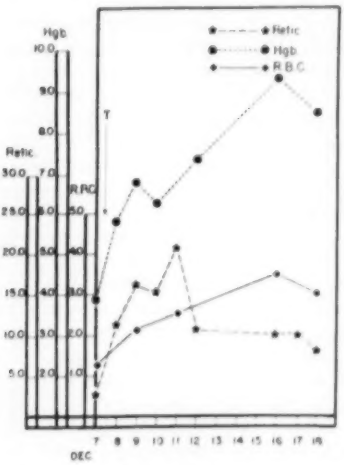

Fig. 4.—Hematologic values in Case 2B.

chronic state by the time of discharge. The leukocytosis and normoblastosis found in her peripheral blood on admission had disappeared on subsequent counts. Her clinical condition remained good and she was discharged 15 days after admission (Fig. 4).

She was seen three months later, having been in good health since her discharge. The liver was 2.0 cm. below the right costal margin, and the spleen was 4.0 cm. below the left costal margin. Her red blood cell count at that time was 2,400,000, with 7.5 gm. of hemoglobin and 23.1% reticulocytes. Her total serum bilirubin was 3.6 mg. per 100 cc., with 0.15 mg. per 100 cc. direct bilirubin.

CASE 3B.—This 2-year-old Negro boy, sibling to the two previously described patients, became ill 2 days prior to admission. At that time he developed signs of an upper respiratory infection, and on the following day it was noticed that he kept his legs in a flexed position. He had never been seriously ill, and sickle-cell disease had never been diagnosed.

On examination he appeared well developed and well nourished but acutely ill with pale conjunctivae. His temperature was 104 F rectally, pulse rate 120, and respirations 20 per minute. His tonsils appeared hypertrophic and hyperemic with a moderate follicular exudate. The ears and nose appeared normal. The heart and lungs were negative to percussion and auscultation. The liver extended 2.0 cm. below the right costal margin, and the spleen was 4.0 cm. below the left costal margin. No abdominal masses or tenderness were present. The remainder of the physical examination was negative.

Laboratory Data.—Urine: negative for albumin and sugar. VDRL, Kahn, and Kolmer and Treponema pallidum immobilization tests were negative. Sickle-cell preparation showed 95% of the erythrocytes to be sickled. Blood: hemoglobin 8.0 gm. per 100 cc.; red blood cells, 2,880,000; white blood cell count, 13,850. Smear: an occasional polychromatophilic cell seen; many target cells and sickle forms. Three nucleated red blood cells were present per 100 white blood cells. Platelets were normal and well clumped. Differential count: neutrophiles, segmented, 76%; bands, 6%; basophilic granulocytes, 1%; lymphocytes, 5%; monocytes, 12%. Reticulocyte count, 6.8%. Direct and indirect Coombs' tests were negative; Van den Bergh: total serum bilirubin, 1.1 mg. per 100 cc. indirect bilirubin, 0.95 mg. per 100 cc.; direct bilirubin, 0.15 mg. per 100 cc. Chest and long-bone x-ray examinations showed no abnormalities.

Course.—Because of the finding of aplasia in another sibling, a bone marrow examination was done on the night of admission (Table). This showed a marrow with slightly decreased cellularity and a relative depression of erythrogenesis for a patient with this type of chronic hemolytic state. There was a decreased number of pronormoblasts and basophilic normoblasts. There was adequate megakaryocytosis. There appeared to be a right shift of the neutrophilic elements and moderate increase in lymphocytes. Serial bone marrows were obtained over the

next 13 days. For the first five days the erythroid elements in the marrow decreased in number. During this period the patient became reticulocytopenic and his hemoglobin dropped to 4.3 gm. per 100 cc. and his red cell count reached a level of 1,340,000. He was given 100 cc. of whole blood on the fifth day and 140 cc. on the following day. His hemoglobin on the day following the transfusion was 6.4 gm. per 100 cc.

On the eighth day after admission to the hospital his marrow showed some improvement, with the presence of a moderate number of pronormoblasts and basophilic normoblasts. Two days after this, reticulocytes appeared in his peripheral blood at a level of 8.3%. The leukocyte count was 25,000, and 75 nucleated red blood cells per 100 white blood cells were present in the peripheral blood at this time. This leukocytosis and normoblastosis subsequently subsided.

The reticulocytes reached a peak of 21.8% on the 12th hospital day. The erythroid elements of the bone marrow at this time were in a hyperplastic state. The patient's hemoglobin after start of the reticulocytosis rose to 9.3 gm. per 100 cc.

The patient remained well after this, and he was discharged on the 16th hospital day (Fig. 5).

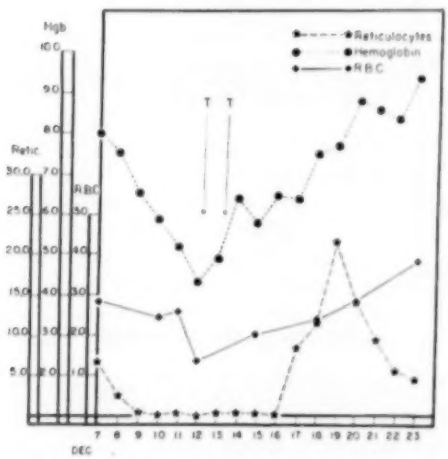

Fig. 5.—Hematologic values in Case 3B.

He was seen again three months later, having been in good health since discharge. His spleen could still be felt 4.0 cm. below the left costal margin. Examination of the blood at that time showed the following: red blood cells, 3,480,000; hemoglobin, 8.9 gm. per 100 cc.; reticulocytes, 9.1%. His total serum bilirubin was 2.0 mg. per 100 cc. with no direct bilirubin present.

The first patient described in the second family returned to the hospital the following month with a hypoplastic crisis. The inclusion of his second hospitalization seems worth while.

Case 1B (Second Admission).—This patient was readmitted to the hospital on Jan. 8, 1956. He had been apparently well since his last discharge until the morning of the day prior to admission. At this time he complained of abdominal pain, vomited several times, and developed fever.

Physical examination revealed the patient to be in moderate distress. His temperature was 104 F. His sclerae were somewhat icteric. His tonsils were large and moderately injected. There were several large submaxillary, nontender nodes in the neck palpable bilaterally. His lungs were negative to percussion and auscultation. There was a Grade III blowing systolic murmur heard all over the precordium but loudest in the third left interspace. The abdomen was diffusely tender, particularly in the left upper and lower quadrants and slightly in the hepatic area. The spleen extended 5 cm. below the left lower quadrant and appeared tender. The liver extended 1 cm. below the right costal margin.

Laboratory Data.—Urine: numerous white cells and 1+ albumin. Subsequent urinalyses were negative. The hemoglobin on that day was 10.1 gm. per 100 cc. Complete blood count the following day was as follows: hemoglobin, 7.4 gm. per 100 cc.; red blood cells, 2,720,000; white blood cells 37,650. Smear: rare polychromatophilic red blood cell seen. No nucleated red blood cells present. Many target cells and sickle forms seen. Reticulocyte count, 3.0%. Differential count: neutrophils, segmented, 88%; bands, 4%, and lymphocytes, 8%. Indirect Coombs' test was negative. The platelet count was 378,080 per cubic millimeter. Van den Bergh reaction on admission revealed a total bilirubin of 3.2 mg. per 100 cc. and a direct bilirubin of 0.90 mg. per 100 cc. Thymol turbidity was 2.5 units.

A chest plate taken on the day of admission revealed the heart to be somewhat enlarged. There was no abnormality of the lungs. Routine stool culture was negative for enteric pathogens. Stool examination revealed no ova and parasites. Three blood cultures grew out only contaminants. Two throat cultures were obtained. Hemolytic Staphylococcus aureus, coagulase positive, was present in the admis-

sion culture, and beta Streptococcus was found in the second one.

Course.—The patient remained moderately ill for the first week of his hospitalization. His temperature ranged between 100 and 104 F despite the use of oral tetracycline. He vomited intermittently and needed supportive intravenous fluids.

Bone marrow examination done on the day after the patient entered the hospital this time did not show as extreme changes as were present on the previous admission (Table). The cellularity was slightly decreased, and rather than severe aplasia of erythroid elements moderate hypoplasia was seen. The megakaryocytic and leukocytic series were normal.

Serial marrow examinations taken three and five days later showed increasing numbers of erythroid cells with a shift toward maturity. His reticulocyte count during this period ranged between 3.0% and 6.2% until the eighth hospital day. During this period his hemoglobin gradually dropped to 4.3 gm. per 100 cc. On the eighth hospital day he was given a transfusion of 220 cc. of whole blood because of the low hemoglobin value. At this time his antibiotic was changed to procaine penicillin because of his persisting fever and the growth of hemolytic Staphylococcus aureus, coagulase-positive, from his throat culture. Twenty-four hours later the patient became afebrile. His reticulocyte count on the eighth day had risen to 11.8% and on the following day reached a peak count of 12.6%. His hemoglobin was 6.5 gm. per 100 cc. the day after his transfusion and remained at about this level for the remainder of his hospital stay. Although a leukocytosis was present in the blood during this patient's illness, no normoblastosis was evident at any time. His condition was improved, and he was discharged on his 21st hospital day (Fig. 6).

He was seen two months later, having been perfectly well in the interim. The liver was not palpable. His spleen was 2.0 cm. below the left costal margin. His erythrocyte count at that time was 2,700,000, with 7.4 gm. per 100 cc. of hemoglobin and reticulocytes of 18.7%. The total bilirubin was 2.9 mg. per 100 cc., with 0.2 mg. per 100 cc. of direct bilirubin.

Paper Electrophoresis

Hemoglobin solutions of the blood of these patients were prepared according to the methods of Singer et al.[5] Using a Durrum type cell and barbital buffer at pH 8.6, paper electrophoresis was performed on the hemoglobin solution of these patients.

The hemoglobin of all five of these patients proved to be pure "S" type by electrophoresis.

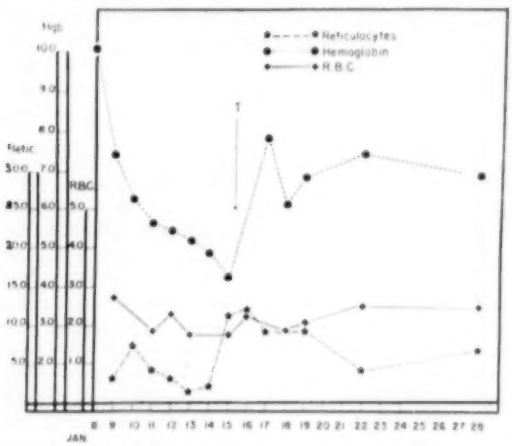

Fig. 6.—Hematologic values in Case 1B (second admission).

Review of the Literature

A curious feature of the hemolytic state, congenital spherocytic anemia, is that several members of a family suffer crises at the same time.[6,9] This has suggested a superimposed infectious agent. In 1948 Owren examined six cases of congenital hemolytic icterus; four of these were from one family. The symptomatology of these patients consisted of fever, rigor, abdominal pain, and vomiting. The temperature became normal

with recovery of the blood picture. Hematologically there was a rapid drop in their hemoglobin and red blood cell count, being about one-half their original value six days from the onset. The icteric color of the serum cleared and reticulocytes disappeared completely from the blood. During the anemic phase examination of the bone marrow showed almost complete aplasia of the erythropoetic tissue. The first sign of recovery was the active formation of large proerythroblasts with the subsequent development of later stages of erythropoesis. The rapid drop in the hemoglobin and erythrocyte values was thought to be due to the shortened survival of the red blood cell found in congenital hemolytic anemia. That same year Dameshek and Bloom [2] reported seven cases of congenital spherocytic anemia with similar episodes. The first three patients were of the same family and lived in the same household. The authors believed that a hypersplenic factor played an important role in the causation of this state because of the finding of "maturation arrest" of the erythroid elements, i. e., large primitive cells and the finding of leukocytic elements and megakaryocytes in the marrow despite a peripheral leukopenia and thrombocytopenia.

The presence of successive cases in the same family suggested to these authors the possible role of infection as a precipitating or trigger agent in initiating an abnormal splenic mechanism leading to crisis.

Sickle-cell anemia is another chronic hemolytic anemia which is characterized by "crises." The exact changes occurring in these situations are to some extent not clear. However, recently it has been realized that the pathogenesis of these attacks is not based completely on hemolysis. Singer et al.[3] in 1950 described an aregenerative crisis occurring in sickle-cell anemia. This occurred in a 9-year-old Negro boy known to have sickle-cell anemia who was admitted with viral pneumonia. He developed erythrocytic aplasia of the bone marrow associated with reticulocytopenia, leukopenia, and slight thrombocytopenia. His hemoglobin and red blood cell count dropped, necessitating a blood transfusion. The patient's sister who was also known to have sickle-cell anemia was admitted to another hospital with similar complaints but did not show signs of an aplastic crisis, since nucleated red blood cells and polychromatophilia were found in the peripheral blood during her illness. The following year Chernoff and Josephson [4] reported similar situations in four Negro children with sickle-cell anemia ranging in age from 30 months to 11.5 years. Siblings of these patients showed no symptoms except for a mild fever in the twin sister of one patient. Salmonella choleraesuis was isolated from the blood of one case and an interstitial pneumonitis was described in another. No hematologic effects were found in the other members of the families. These same authors also described a patient with infectious mononucleosis who had a superimposed red blood cell aplasia.

Along these same lines Gasser [10] has described 10 children between the ages of 1.5 years and 12.5 years with acute "erythroblastopenia." Only one child had an intrinsic blood disease, congenital spherocytic anemia. He described a transitory erythroblastopenia of the marrow in a nonanemic patient with atypical pneumonia. This author found erythrocyte aplasia in various conditions, such as diphtheria, allergic reactions to drugs (phenobarbital [Luminal], chenopodium oil [oleum chenopodi]), after an insect bite, and in patients with anaphylactoid purpura. The aplastic crisis usually lasted about one week and was accompanied by reticulocytopenia and sometimes by moderate leuko- and thrombocytopenia in the peripheral blood. These observations suggest that the aplasia of the erythropoetic tissue may not only be caused by infective agents but also may develop on a toxic or allergic basis.

Since the reports by Singer et al. and Chernoff and Josephson, no others have been published concerning the aplastic crisis of sickle-cell anemia.

The case reports of four patients of two families with sickle-cell anemia, complicated by aplastic crisis, are reported here. There

were two patients from each family. The onset of these crises appeared within a two-week period in each set of patients. One of the patients (Case 1B) was admitted to the hospital on two separate occasions. During the latter hospitalization he appeared to have a hypoplastic rather than an aplastic crisis. Another member (Case 2B) of this same family is also reported. She appeared to be at the end of her aplastic crisis and just beginning to have her reticulocytosis. She will be discussed below.

The remaining siblings of both families were examined for sickle-cell disease. In Family B two sisters were found to have the trait. In the other family the patient's sister showed no stigmata of sickle-cell disease. None of these siblings were ill during the period of crises of the patients described.

Infectious Aspects.—To our knowledge this is the first time that aplastic crises have been reported to occur in siblings with sickle-cell anemia within a short period of time. This suggests that an infectious agent is involved in their causation. With this thought in mind, attempts were made to isolate a causative viral or bacteriologic agent. Routine throat, blood, and stool cultures were taken for bacteriologic examinations.

Hemolytic Staphylococcus aureus, coagulase-positive, was cultured from the throat of patient in Case 3B several days after his admission. This may have been transmitted to him from another patient in the hospital who was harboring this bacteria, since it was not present on his admission culture.

On the second admission of the patient in Case 1B throat culture grew the above-mentioned organism and subsequent pharyngeal culture showed beta-hemolytic Streptococcus. This latter organism may also have been acquired after admission to this hospital. Other than this no pathogenic bacteria could be found.

Antistreptolysin titer done on all patients showed no elevation except in the patient in Case 1B (166 Todd units). However, as there was no significant quantitative change in the titer during his two admissions and two months after his second admission, it was felt that this finding was probably not related to his two crises.

Heterophile and cold agglutination titers were done on all of the patients and showed no significant titers.

The Treponema pallidum immobilization test was positive in Case 1B, and he was felt to have latent congenital syphilis. This infection probably has no relationship to the situation at hand.

Stool specimens, bone marrow, and throat swabbing in saline solution taken at the time of their acute illness were frozen and later tested for the presence of specific and unselected viruses.* According to the procedures done it can be reasonably certain that there were no significant amounts present of adenoidal-pharyngeal-conjunctival, herpes simplex, some strains of influenza B, poliomyelitis, certain B Coxsackie, or ECHO viruses.

Comment

The occurrence of these attacks in several members of the same family, the associated respiratory infections seen, and the finding of plasma cells in the blood and bone marrow in several of these patients are all highly suggestive of an infectious agent. The only bacteria found in more than one patient was the hemolytic Staphylococcus aureus, coagulase-positive. This was seen in two members of Family B but was not found at the same time and in the one patient may have been acquired after admission to the hospital. It is difficult to derive any real association from these findings. Therefore, for the group as a whole no common agent was present, most showing no pathogenic organisms at all.

The possibility remains that some hitherto unrecognized organism may be present. However, the most reasonable explanation, fitting most of the observed facts, would be that no single organism is responsible. This would fit the observations of aplastic crises occurring in Singer's patient with virus

* Dr. Robert Parrott of the Microbiologic Institute of the National Institutes of Health performed these examinations and provided helpful suggestions.

pneumonia, the patient of Chernoff and Josephson with S. choleraesuis infection,[7] and with Gasser's studies.

Pathogenetic Mechanisms

The anemia of chronic hemolytic disease in the uncomplicated situation is due to the shortened survival of the erythrocyte.[11] To compensate for the increased elimination of the cells, the marrow must regenerate at an accelerated rate. It has been shown by Crosby and Ackeroyd[12] and by Giblett et al.[13] that in chronic hemolytic disease the capacity of the marrow to produce erythrocytes may increase its activity six- to eightfold. If the survival of red blood cells becomes further shortened so that a sixfold increase in the production of red blood cells does not equal the numbers of disappearing erythrocytes, the red blood cell count and hemoglobin level will fall.

Owing to apparent extrinsic factors a different complication occurs in the aplastic crisis. It appears that the survival of red blood cells is probably not further shortened during the aplastic crisis, but that the compensatory mechanisms are impaired. There is a generalized diminution in marrow erythropoesis, and a subsequent absence of reticulocytes. This period may last up to 10 days.[4] The longest period in our patients was nine days. During this aregenerative period the erythrocyte and hemoglobin level dropped owing to the elimination of intrinsically defective red blood cells of sickle-cell anemia. If the life span of the sickle cells were all uniform then at the end of that specific time no erythrocytes would be present. However, it has been shown that there is considerable variability in the life span of these cells.[3,11] Thus in these patients with aregenerative crises one can expect an initial rapid fall in red blood cell numbers followed by a later slower decline. The phenomenon of the variable destructibility of different proportions of the red blood cell population in sickle-cell anemia explains why in the absence of any cell replacement the erythrocyte count will show a rather precipitous fall in some patients and a less distinct decrease in others.

The aplastic crisis is therefore dependent on two conditions, namely, the complete cessation of erythrocyte production and the shortened survival of the red blood cell. The severity of the crisis will be directly proportional to the number of easily destructible erythrocytes present in the total erythrocyte population. Conversely, when erythroblastopenia occurs in a disease such as infectious mononucleosis, where the life span of the red cell is normal, its effects may take some time to become evident.[4]

In Cases 3B and 1B (second admission), who were in the early stage of their crises on admission and who did not receive transfusions at that time, there was an approximate 50% drop in their red blood cell and hemoglobin values in a five- and seven-day period, respectively. In the other patients transfusions were given shortly after they were hospitalized to alleviate anemia. Because of the normal life span of the transfused cells further depression of the hemoglobin levels did not occur to any extent.

Morphologic Aspects

The most diagnostic and pathogenetic feature of the aplastic crisis of the patient with sickle-cell anemia is the decrease in the number of erythroid precursors in the bone marrow. A few pronormoblasts may be seen, but more mature cells are virtually absent. Large basophilic cells of the erythroid series with a diameter up to 60μ have been described, closely resembling pronormoblasts in nuclear structure and staining characteristics.[1,2,10] These were not noted in the marrow of our patients. On the basis of the differential counts done on the marrow during the erythroblastopenic phase there was no increase in pronormoblasts. This would make the possibility unlikely of a maturation arrest at this level due to splenic activity.

Cytologic changes were noted in the late marrow normoblasts of cases 1A and 3B during the early stage of their aregenerative

crises. These consisted of irregular clumping of nuclear and cytoplasmic substances. There was fragmentation of the nuclear and cell borders. Fine and some coarse cosinophilic bodies were present in the cytoplasm of the polychromatic normoblasts as well as a few solitary basophilic stipples. The mechanism for these changes is obscure.

The aregenerative crisis may last as long as 10 days. Within four days after the marrow shows evidence of regeneration, the release of reticulocytes may be expected.

In several patients normoblasts were found in the peripheral blood as reticulocytosis began. This was due to the shift of cells from the marrow reservoir into the blood.[13] Thrombocytopenia and/or leukopenia were not found in the blood of any of our patients.

It is interesting to note that the patient in Case 1B returned approximately one month after discharge with symptoms usually found in a crisis of sickle-cell disease with a possible splenic infarction. On this occasion erythropoesis did not appear to be as diminished as on his previous episode and the reticulocytes never completely disappeared from the peripheral blood. This would indicate that these crises may not be an absolute situation but show various degrees of severity. It is difficult to state whether some patients are more prone to this type of attack. Only future observations can determine this.

Case 2B is included in this series to suggest the possibility that it may be difficult at times to ascertain with one observation whether an aplastic crisis has occurred. This patient on admission demonstrated a reticulocytosis and a marked normoblastosis with an extremely hyperplastic marrow. From these facts and the rising hemoglobin over a nine-day period, with only one small transfusion, and the consistent reticulocyte rise, it can be assumed that an aplastic crisis had been present in this person.

Summary

The aplastic crises of sickle-cell anemia which developed within a short period of time are described in members of two different families. Another member of one family is reported because she was suspected of having a similar condition. One of the patients described returned one month later in a "hypoplastic" state. All of these patients did well with transfusion and general supportive therapy.

A search was made for a bacteriologic or viral agent which might have played an etiologic factor in the causation of this erythroblastopenia. No specific organism could be found which might be associated with this syndrome.

District of Columbia General Hospital.

REFERENCES

1. Owren, P. A.: Congenital Hemolytic Jaundice: The Pathogenesis of the "Hemolytic Crisis," Blood 3:231-248, 1948.

2. Dameshek, W., and Bloom, M.: The Events in the Hemolytic Crisis of Hereditary Spherocytosis, with Particular Reference to the Reticulocytopenia, Pancytopenia and an Abnormal Splenic Mechanism, Blood 3:1381-1410, 1948.

3. Singer, K.; Motulsky, A. G., and Wile, S. A.: Aplastic Crisis in Sickle Cell Anemia: Study of Its Mechanism and Its Relationship to Other Types of Hemolytic Crises, J. Lab. & Clin. Med. 35:721-735, 1950.

4. Chernoff, A. I., and Josephson, A. M.: Acute Erythroblastopenia in Sickle-Cell Anemia and Infectious Mononucleosis, A. M. A. Am. J. Dis. Child. 82:310-322, 1951.

5. Singer, K.; Chernoff, A. I., and Singer, L.: Studies on Abnormal Hemoglobins: I. Their Demonstration in Sickle Cell Anemia and Other Hematologic Disorders by Means of Alkali Denaturation, Blood 6:413-428, 1951.

6. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1951, p. 599.

7. Dameshek, W.: Familial Hemolytic Crisis, New England J. Med. 224:52-56, 1941.

8. Horne, J. L.; Lederer, J.; Kirkpatrick, H. J. R., and Leep, D.: Familial Crisis in Congenital Hemolytic Disease, Lancet 2:33-36, 1945.

9. Marson, F. G.; Meynell, M. J., and Tabbush, H.: Familial Crisis in Acholuric Jaundice, Brit. M. J. 2:760-761, 1950.

10. Gasser, C.: Akute Erythroblastopenie; 10 Fälle aplastischer Erythroblastenkrisen mit Riesenproerythroblasten bei allergisch-toxischen Zustandsbildern, Helvet. paediat. acta 4: 107-143, 1949.

11. Callender, S. T. E.; Nickel, J. F.; Moore, C. V., and Powell, E. O.: Sickle Cell Disease: Studied by Measuring the Survival of Transfused Red Blood Cells, J. Lab. & Clin. Med. 34:90-104, 1949.

12. Crosby, W. H., and Ackeroyd, J. H.: The Limit of Hemoglobin Syntheseis in Hereditary Hemolytic Anemia: Its Relation to Excretion of Bile Pigment. Am. J. Med. 13:273-283, 1952.

13. Giblett, E. R.; Coleman, D. H.; Pirzio-Biroli, G.; Donahue, D. M.; Motulsky, A. G., and Finch, C. A.: Erythrokinetics: Quantitative Measurements of Red Cell Production and Destruction in Normal Subjects and Patients with Anemia, Blood 11:291-309, 1956.

Chronic Renal Tubular Insufficiency in Infants and Children

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Renal tubular insufficiency exclusive of tubular insufficiency attributed to chronic pyelonephritis and hydronephrosis is infrequently encountered in pediatric practice. Nevertheless, an increasing number of clinical syndromes have been ascribed to such insufficiency, and the pediatrician must be aware of their existence. A continuous search for these diseases may enable him to make an accurate diagnosis and to institute palliative or even curative therapy. The syndrome of acute renal tubular failure is usually recognized by sudden onset of oliguria or anuria in association with crush injuries, transfusion reactions, ingestion of poisons, or sulfonamide administration, and is not considered in this presentation. In contrast, the syndromes of chronic renal tubular insufficiency are more insidious in their onset and should be suspected in infants and children who fail to thrive and who have polyuria, polydipsia, thermolability, or rickets.

With few exceptions, the chronic affections of the renal tubules have been described during the last 20 years. Originally they were reported as isolated entities but recently many authors have attempted to classify the diseases. An accurate etiologic classification is impossible, since the cause in most instances is unknown or is considered to be a hereditary process. Myerson [1] and Pastor have classified the diseases according to the symptoms they produce. Dent [2] classified them, when associated with rickets, according to the functional abnormalities of the renal tubule (Table). Fanconi [3] classified them according to the probable site of the lesion in the nephron. His classification appears to be the preferable one despite the fact that the alleged anatomic localization may not be correct in every instance. We are also aware that there may be considerable overlapping among the disease entities. The advantage of his type of classification is that it enables one to visualize the various diseases in the light of present knowledge of renal tubular physiology. A modification of the scheme described by Fanconi is shown in the Figure. Because the primary pathologic changes in glomerular nephritis and nephrosis are in the glomerulus, they will not be discussed in this paper.

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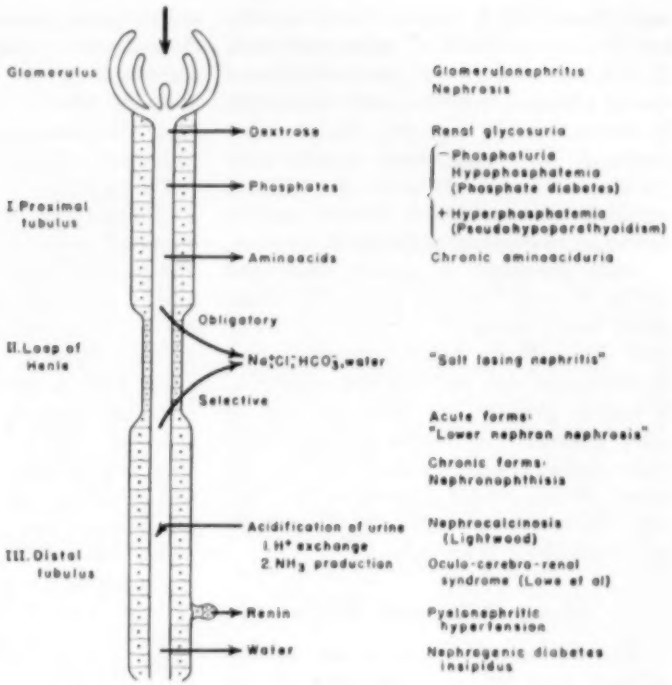
Renal Glycosuria

Reabsorption of glucose, phosphates, and amino acids takes place primarily in the proximal renal tubules. If reabsorption of glucose alone is inadequate, glucose is lost in the urine and renal glycosuria results. Klemperer [4] and Lépine,[5] in 1896, were the first to recognize glycosuria in a nondiabetic person with a normal level of blood sugar. Bönniger,[6] in 1908, presented a well-documented case of renal glycosuria. That the condition is infrequent is attested by the fact that only 3.11% of 14,000 patients with glycosuria seen at the Joslin Clinic were found to have renal glycosuria.[7]

It appears fairly well established that renal glycosuria is a familial disease transmitted as a dominant characteristic.[8,9] The pathologic changes have been reported in only one case. Monasterio [10] described vary-



Classification of chronic diseases of the renal tubules according to the probable site of the lesion in the nephron (modified from Fanconi [8]).

ing degrees of dilatation of the renal tubules and flattening of the tubular epithelium in a biopsy specimen taken from the kidney of a 36-year-old woman with renal glycosuria.

It is generally accepted that the functional defect in renal glycosuria is an inability of the tubules to reabsorb that glucose which is filtered by the glomeruli in the presence of normal levels of blood sugar. Friedman and co-workers [11] studied two adult patients with renal glycosuria and noted that the efficiency of tubular reabsorption of glucose equalled or exceeded that found in nonglycosuric persons in whom the level of glucose in the plasma was more than 200 mg. per 100 ml.

Marble [12] listed the following criteria as essential in establishing the diagnosis of

Rickets or Osteomalacia Associated with Defects of Tubular Function (from Dent)[9]

Type	Defect in Tubular		Names Used to Describe Syndromes
	Reabsorption	Function	
1	Phosphate		Resistant (*or refractory*) rickets, raised late rickets, resistance to vitamin D (RRD), essential hypophosphatemic rickets, idiopathic osteomalacia, Milkman's syndrome
2	Phosphate Glucose		
3	Phosphate Glucose Amino acids Water*		Fanconi syndrome, Debre-de Toni-Fanconi syndrome, Lignac's disease, cystine rickets, cystinosis, rickets with cystinuria, aminidiabetes, diabetes aminicus et acidaminicus, "renal rickets," (?) hepatic rickets, hypophosphatemic glycosuric rickets
4	Phosphate Glucose Amino acids Water* Potassium*	Acidification of urine	
5	Phosphate Potassium*	Acidification of urine	Nephrocalcinosis with renal rickets and dwarfism, hyperchloremic nephrocalcinosis, Butler-Albright syndrome, renal tubular acidosis
6	Phosphate Potassium*	Acidification of urine Ammonia formation	

*Defect not always conspicuous.

renal glycosuria: 1. Glucose should be present in every specimen of urine examined. 2. The level of the blood sugar should not exceed 120 mg. per 100 ml. while the patient is fasting, or 170 mg. per 100 ml. after meals. 3. The characteristic symptoms of diabetes mellitus should be absent. 4. There should be no transition to diabetes mellitus during an observation period of three years.

Renal glycosuria is usually discovered during the first 2 decades of life but recognition before the age of 5 years is extremely rare. Although the disease occasionally may be associated with polyuria and polydipsia, it usually produces no symptoms and, in most instances, is discovered accidentally when glucose is found in the urine. The disease is benign and not progressive. No therapy is necessary, although an adequate intake of carbohydrate is advised.

Vitamin D-Resistant Rickets

This disease, which may be the result of primary renal tubular insufficiency, is also known as phosphate diabetes, essential hypophosphatemic rickets and idiopathic osteomalacia. It may present all of the usual clinical features of simple vitamin D-deficiency rickets. It was first recognized as a distinct clinical entity by Albright, Butler, and Bloomberg [13] in 1937. The important fact regarding the disease is that large doses of vitamin D are necessary to produce a good therapeutic response. Untreated or inadequately treated patients are usually dwarfed and may have enlargement of epiphyses, frontal bossing, occipital protuberances, and genu valgum or genu varum. Pedersen and McCarroll [14] reported observations on 25 patients with vitamin D-resistant rickets and noted that these patients present many features that suggest chondrodystrophy. Although sporadic cases are noted, the disease is thought to be familial.

Freeman and Dunsky,[15] Fanconi and Girardet,[16] and others have considered vitamin D-resistant rickets to be the result of a specific inability of the proximal renal tubules to reabsorb proper amounts of phosphates in the presence of adequate antirachitic doses of vitamin D. This inability is correctable by the administration of large doses of vitamin D. There have been no reports of pathologic studies of the kidneys of patients with this disease.

The significant laboratory findings include a decreased level of serum phosphate and an increased excretion of urinary phosphate. The level of serum alkaline phosphatase is usually increased while the level of serum calcium is normal or decreased. In some patients there is increased excretion of amino acids in the urine.

Roentgenograms of the bones show evidence of rickets; the epiphysial lines are wide and the zone of calcification is fuzzy and indistinct. There usually is generalized osteoporosis, and the cortex of the long bones may be thin.

Treatment consists of the administration of large doses of vitamin D. According to Dent,[2] treatment should begin with 50,000 units of vitamin D given daily, and the dose should be gradually increased until the level of phosphate rises to 2.5 or 3 mg. per 100 ml. of serum. Following this the lowest possible dose that will maintain the serum phosphate at this level is determined. As much as 500,000 units a day is necessary in some cases. Vitamin D intoxication may be induced; therefore, it is necessary to determine the level of the serum calcium at frequent intervals during the period of regulation. If the level exceeds 11 mg. per 100 ml., the administration of vitamin D is discontinued until it returns to normal and then administration of the drug is started again in a smaller dose. The occurrence of anorexia, nausea, polyuria, and polydipsia suggests vitamin D intoxication and should prompt a determination of the levels of the serum calcium.

Vitamin D-Resistant Rickets with Glycosuria.—A few cases of vitamin D-resistant rickets and renal glycosuria have been reported. In the case reported by Cooke and associates,[17] the patient died at the age of 39 years. Microscopic examination of the

kidneys showed pronounced vacuolization and occasionally necrosis of the proximal convoluted tubules.

Pseudohypoparathyroidism

Parathyroid hormone exerts its physiologic effect, at least in part, by decreasing reabsorption of phosphates by the renal tubules. In the absence of parathyroid hormone, excessive amounts of phosphates are reabsorbed by the renal tubules and hyperphosphatemia results. Albright and associates [18] were the first to recognize that certain patients with a clinical syndrome suggestive of hypoparathyroidism did not have a phosphate diuresis following the administration of parathyroid hormone. These observers ascribed the disorder to failure of the renal tubules to respond to parathyroid hormone.

The clinical features of pseudohypoparathyroidism are similar to those noted in hypoparathyroidism except that patients with the former condition have associated developmental abnormalities, including a rounding of the face and a shortening of the metacarpal and metatarsal bones. Dwarfism of moderate to marked degree also may be noted. Hypocalcemic tetany, muscle spasm, convulsions, and, in some cases, rather marked mental retardation prompt the patient to seek medical care. If the condition remains untreated, progressive mental deterioration, cataract formation, and convulsions ensue.

Laboratory determinations in pseudohypoparathyroidism reveal elevation of the level of phosphate and decrease of the level of calcium in the serum. The disease is distinguished from true hypoparathyroidism by the absence of phosphate diuresis after parathyroid hormone is administered (Ellsworth-Howard test).

Treatment consists of the administration of dihydrotachysterol (A.T. 10) alone, or in combination with soluble calcium salts, to maintain the serum calcium at a level of 8 or 9 mg. per 100 ml. In most instances, daily administration of 50,000 to 100,000 units of vitamin D or 0.625 to 1.25 mg. of dihydrotachysterol and 5 to 20 gm. of calcium lactate (previously dissolved in hot water) is sufficient to control the hypocalcemia. Treatment for the cataracts should be delayed until after the hypocalcemia has been corrected.

Fanconi's Syndrome

Fanconi's syndrome, also known as Debré-de Toni-Fanconi syndrome, diabetes aminoacidus and chronic amino-aciduria, is a disorder characterized by a disturbance of renal tubular function resulting in decreased reabsorption of glucose, phosphates, amino acids and fixed base. Although the striking clinical picture presented by patients with this disease was noted by several observers, it was not until 1936 that Fanconi [19,20] recognized it as a nosologic entity and attributed the pathologic physiology to isolated renal tubular dysfunction. The observations of Fanconi have been confirmed and extended by others.

The pathologic changes observed in patients with Fanconi's syndrome are confined largely to the proximal part of the renal tubules. Clay and associates [21] did microdissections of nephrons of two patients with the disease and were able to demonstrate marked narrowing and atrophic changes in the proximal tubules. Two observers,[22] using histochemical techniques, found decreased amounts of alkaline phosphatase in the proximal renal tubules of patients with Fanconi's syndrome. Harrison and Harrison [23] produced glycosuria, aminoaciduria, and phosphaturia in rats by administration of maleic acid. Cystinosis, a rare disease considered to be the result of an inborn error of protein metabolism characterized by abnormal deposition of cystine crystals in body tissues including the tubules of the kidneys, may manifest itself as Fanconi's [24] syndrome. Thus it appears that the renal tubular damage characteristic of this syndrome may result from several causes. It is well established that in many cases Fanconi's syndrome is a hereditary disease; the

milder forms are transmitted as a dominant characteristic, the graver forms as a Mendelian recessive. We believe that the disease may be the result of an inherited defect in the tubules, destruction of the tubules by cystine crystals, or perhaps other as yet unexplained causes.

The clinical features of Fanconi's syndrome are fairly constant. The disease is most frequently observed in children between 1 and 2 years of age. Most of the children with the disease are considered to be normal during the first few months of life, but anorexia, failure to gain weight, weakness, irregular bouts of fever, constipation, polyuria, and polydipsia appear before the end of the first year. The irregular fever often leads to the suspicion of sepsis. As the disease progresses, weakness, wasting, dehydration, rickets, and dwarfism become marked. Anorexia may be extreme and vomiting may follow ingestion of even small amounts of solid food. Polydipsia likewise may be extreme, leading to the erroneous diagnosis of diabetes insipidus. It should be realized that the disease may vary considerably in severity and that milder forms may be manifested clinically by little more than rickets and dwarfism. Variation in the manifestations of the disease is assumed, but not proved, to be due to variation in the location and severity of the tubular defect.

Laboratory findings in patients with Fanconi's syndrome are striking. The level of urea in the blood is usually normal and remains normal until late in the disease, when glomerular failure occurs. Values for serum phosphate, serum potassium, and carbon dioxide combining power of the plasma are low, while values for serum sodium and serum calcium remain normal. The value for serum chloride is usually elevated. As would be anticipated in patients with severe rickets, the value for alkaline phosphatase is elevated. The urine has a low specific gravity and is neutral or alkaline even in the presence of hyperchloremic acidosis (in the blood). Glycosuria is almost always present. There is a marked increase in the excretion of amino acids in the urine.

Radiologic examination shows evidence of active rickets with pseudofractures, deformities, or, occasionally, true fractures.

In every patient with Fanconi's syndrome, cystine crystals should be searched for. Several techniques for demonstrating their presence have been described. These include examination of the corneas by means of the slit lamp and microscopic examination of a properly prepared biopsy specimen of lymph node, bone marrow, or conjunctiva.

The treatment of Fanconi's syndrome is far from satisfactory, but the pessimism of earlier observers is no longer justified. The aim of treatment is to compensate for the excessive losses of amino acids, phosphates, water, glucose and fixed base. In 1947, Stowers and Dent [22] reported that the administration of large doses of vitamin D resulted in an elevation of serum phosphates and in clinical improvement. Bickel and Smellie [24] noted that the condition of a group of patients with cystinosis was improved after the administration of vitamin D, potassium chloride, and a mixture of sodium citrate and citric acid. Salassa and co-workers [25] observed increased reabsorption of glucose, phosphates, and amino acids and improvement in the hyperchloremic acidosis and osteomalacia following the administration of vitamin D to two patients, aged 11 and 16 years. Both of these patients have remained in good health, although it has been necessary to reduce the dose of vitamin D. It should be emphasized that the results of treatment depend on many factors, and it is not implied that every patient with Fanconi's syndrome will respond satisfactorily to treatment. Worthen and Good,[26] in a recent publication, said they were unable to obtain a satisfactory response to vitamin D in one patient with Fanconi's syndrome.

Anderson and co-workers[27] induced retention of calcium, phosphorus, and nitrogen in patients with Fanconi's syndrome by the administration of methyl testosterone.

In summary, it may be stated that each patient with renal tubular failure should be carefully evaluated and every effort should be made to correct the altered physiology by providing the patient with enough alkali to correct the acidosis, enough fluids to prevent dehydration, enough potassium to prevent hypopotassemia, and perhaps enough vitamin D to correct the rickets. This may be accomplished only by the slow process of trial and error.

It should be mentioned here that increased excretion of amino acids in the urine has been observed in patients with various diseases. The relation of amino-aciduria to the primary disease is not understood in most instances and the condition may represent only a coincidental finding. Jonxis[28] has demonstrated aminoaciduria in patients with simple vitamin D-deficiency rickets. He also observed that some members of the families of patients with simple rickets excreted increased amounts of amino acids in the urine, although they manifested no evidence of rickets. Scurvy may also be accompanied by increased excretion of amino acids.

Hereditary cystinuria, a disease considered to be the result of an error in cystine metabolism, is also characterized by increased excretion of cystine. In other cases, there are increased amounts of arginine, lysine, and ornithine in the urine.

Infants suffering from galactosemia excrete increased amounts of amino acids in the urine, in addition to large amounts of galactose. In these patients the aminoaciduria appears to be related to the galactosuria, since the excretion of amino acids decreases as the excretion of galactose is reduced by elimination of this substance from the diet. Some patients with phenylpyruvic oligophrenia have been shown to excrete an increased amount of a variety of amino acids in their urine.[3]

Salt-Losing Nephritis or Diabetes Salinus Renalis (Fanconi)[29]

In an occasional patient with advanced renal disease the tubules may lose their ability to reabsorb adequate amounts of sodium chloride. The danger of fatal losses of salt is especially great if glomerular function is adequate. Since this condition is a manifestation of more serious renal disease, treatment depends on the primary condition plus the administration of salt to replace that which is lost.

Familial Juvenile Nephronophthisis

Fanconi,[3,29] in 1951, reported observations on eight children from two families with a disease that he named "familial juvenile nephronophthisis." The clinical features were remarkably similar in all cases. Polyuria, polydipsia, and nocturia appeared at about the age of 2 years. As the disease progressed, oliguria ensued and three of the patients died of uremia at the age of 6 years. Laboratory studies disclosed persistently low values for blood sugar and hyperelectrolytemia. Albuminuria was not noted early in the course of the disease. Terminally, all signs of glomerular failure became apparent. Histologic examination of the kidneys from the patients who died of the disease disclosed degeneration of the renal parenchyma marked by hyaline changes in the epithelium of the proximal convoluted tubules and the basal membrane. There was hyaline degeneration of the glomeruli without evidence of inflammatory changes or sclerosis of the arterioles. Fanconi considered the early manifestations of the disease to be a result of primary renal tubular insufficiency. We have encountered no other reports of this unusual condition.

Infantile Renal Acidosis or Lightwood-Albright Disease

One of the most important functions of the kidney is regulation of the acid-base balance, a function that appears to be accomplished in large part by the distal renal

tubules. Acid-base equilibrium is probably maintained by two separate mechanisms, namely hydrogen-ion exchange and ammonia production, both of which aid in conserving fixed base. Should these mechanisms fail, fixed base is lost and acidosis ensues.

Lightwood,[31] in 1936, called attention to a clinical syndrome which he attributed to isolated failure of the base-preserving function of the distal tubules. In 1940, Albright and co-workers[32] described a similar syndrome in adults. The observations of these workers have been confirmed by many others, and the syndrome of infantile renal acidosis or Lightwood-Albright disease, as the condition is called in adults, has become a well-established clinical entity.

The cause of infantile renal acidosis is unknown but many hypothetical causes have been suggested. These include selective damage to the distal tubules by infections, poisons (for example, mercury or sulfonamides), or dehydration. More recently, Lightwood and co-workers[33] have suggested that the disease as seen in infants might be the result of functional immaturity of the kidney. None of these theories have been proved, and available evidence suggests that the disease may be caused by any one of several factors.

Infantile renal acidosis was recognized by Lightwood at the time he reviewed the records of 850 consecutive necropsies done on infants and children. He observed deposits of calcium extending from the apexes of the pyramids to the cortex in six cases, and on microscopic examination of these kidneys he noted the calcium to be deposited in the collecting tubules. A review of the records disclosed that these patients had died of diseases that were remarkably similar, and that acidosis had been present in all cases in which appropriate laboratory data were available. He has since been able to collect a total of 35 cases of the disease from the pediatric service of the Hospital for Sick Children in London. Thus the disease is undoubtedly commoner than is generally recognized.

There is no agreement as to the exact site of the renal lesion that produces infantile renal acidosis. It is agreed, however, that only a part of the acid-base regulating mechanism is disturbed, since there is some production of ammonia. As Schreiner and associates[34] have observed in adults with the disease, the defect could be the result of (1) failure of the distal tubular exchange of H ions or (2) primary failure of reabsorption of bicarbonate by the proximal tubules or (3) primary increase in reabsorption of chloride or (4) a combination of (1) and (2).

The clinical manifestations of infantile renal acidosis are usually not manifest until the infant is 6 to 12 months old. It is first noted that the infant fails to thrive. Vomiting and constipation may be present. Polyuria and polydipsia, which are constant features of the disease in adults, are usually not observed in infants, although infants often prefer liquid to solid foods. The disease occurs about twice as frequently in males as in females.

Physical examination may show no gross abnormalities, but some children are wasted, have muscular hypotonia, and are listless. Signs of acidosis and dehydration are observed infrequently.

Laboratory studies characteristically disclose an increase of the serum chlorides and a decrease of the carbon dioxide combining power. The levels of the serum sodium and serum potassium may be decreased while the level of the blood urea is normal except during periods of dehydration. The specific gravity of the urine is low, varying between 1.005 and 1.010, and the urine may contain small amounts of protein and a few leukocytes. The reaction of the urine is almost always neutral or alkaline, although it may occasionally be acid in patients with severe dehydration. The ammonia content of the urine is diminished or normal. As noted previously, Lightwood and associates became interested in this disorder because of the finding of calcium in the kidneys. Roentgenologic evidence of varying degrees of

renal calcification was noted in 13 of the 35 patients mentioned in his recent publication. Renal calcifications appear to occur more frequently in adult patients with the Lightwood-Albright syndrome. In an occasional child there may be roentgenologic evidence of rickets.

The treatment of infantile renal acidosis consists primarily of the administration of alkalies, either as sodium bicarbonate or as a buffered solution. Lightwood recommends a mixture of sodium citrate (10 gm.) and citric acid (6 gm.) in water (100 ml.). Alkali should be given in whatever dose is necessary to correct the acidosis. Treatment should be continued until the infant is gaining weight normally and the carbon dioxide combining power of the plasma has been more than 20 mEq. per liter for at least three months. Results of treatment are usually quite striking, and recovery is to be anticipated with continued treatment.

Oculocerebrorenal Syndrome

Lowe and co-workers [35] and, more recently, Worthen and Good [26] have noted infants with multiple abnormalities, one of which is renal tubular insufficiency. The infants exhibit hyperactivity, flabby musculature, an abundance of subcutaneous fat, hyporeflexia, hydrophthalmos, mental deficiency, intermittent bouts of fever of undetermined cause, and, in some cases, cataracts and rickets.

Disturbances in the concentration of serum electrolytes that accompany the disease are attributed to an inborn error in metabolism resulting in the production of excessive amounts of organic acids which must be excreted. In addition, the patients appear to have impaired renal tubular function characterized by decreased production of ammonia. As a result, the carbon dioxide combining power of the plasma is decreased while the level of serum chloride is at the upper limit of normal or slightly elevated. The urine contains increased amounts of protein and decreased amounts of ammonia.

Treatment is directed toward correction of the acidosis by the administration of buffered alkali. Patients with rickets are benefited by the addition of small doses of vitamin D. Hydrophthalmos and cataracts require surgical management. Unfortunately, mental deficiency, which is the most disturbing feature of the disease, is not altered by treatment.

Pyelonephritic Hypertension

Fanconi [3] has reported interesting observations on two patients seen 11 and 19 years, respectively, after they had been observed with hypertension and pyelonephritis. In each instance, hypertensive changes that had been found in the optic fundi at the time of the original examination had disappeared by the time of the examination made years later. The author concluded that transient hypertension had been the result of inflammatory reaction about the renin-producing cells of the distal tubules, and for this reason we mention the syndrome in this discussion for completeness.

As a result of inflammation the renin cells were stimulated to secrete renin which was converted by the liver to hypertensinogen which in turn produced the hypertension.

Nephrogenic Diabetes Insipidus

Veil,[36] in 1923, postulated the existence of a type of diabetes insipidus that would not respond to the administration of vasopressin (β-Hypophamine) (Pitressin) tannate but did not describe a patient with such a disease. Haymann and Fanconi,[37] in 1926, appear to have been the first to describe a patient with vasopressin tannate-resistant diabetes insipidus. Waring and associates,[38] in 1945, gave a detailed description of the disease and reported their observations on six patients. Several reports [39-42] have appeared during recent years, and the disease entity is well established. The functional defect is attributed to an inability of the distal tubules to reabsorb water in response

to antidiuretic hormone from the posterior pituitary. Pathologic studies of the kidneys of patients with this disease have shown mild hydronephrosis and dilatation of the tubules containing eosinophilic hyaline casts.

The disease occurs almost exclusively in males although it has been recognized in a few females. It is a familial disease but the pattern of transmission apparently varies in different families.

Polydipsia and polyuria, which are so characteristic of this disease, usually appear soon after birth. Vomiting not infrequently follows the ingestion of large volumes of liquids. Constipation is often a disturbing symptom. Dehydration may be so severe as to result in hyperthermia. These patients may drink almost unbelievable amounts of liquids. When deprived of liquids they become extremely irritable and dehydration ensues rapidly.

The results of laboratory tests, except for low specific gravity of the urine, are of little help in establishing the diagnosis, although they may be of great value in excluding other disorders associated with polyuria. Occasionally, special studies such as that devised by Hickey and Hare [43] may be necessary to distinguish between nephrogenic diabetes insipidus, true diabetes insipidus, and functional polydipsia. During periods of dehydration with hemoconcentration the level of serum sodium and chloride may be elevated. The results of urinalysis are normal except for low specific gravity (not exceeding 1.005). The administration of vasopressin tannate does not alter the clinical course of the disease or produce a significant rise in specific gravity of the urine.

Treatment is unsatisfactory, since nothing is known that will control the constant loss of water in the urine. In small infants it is frequently necessary to dilute the formula with water so that an adequate intake of fluid can be maintained. The prognosis is usually good, although the disease persists unchanged throughout life. An occasional patient may have impaired growth.

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REFERENCES

1. Myerson, R. M., and Pastor, B. H.: The Fanconi Syndrome and Its Clinical Variants, Am. J. M. Sc. 228:378-387 (Oct.) 1954.

2. Dent, C. E.: Rickets and Osteomalacia from Renal Tubule Defects, J. Bone & Joint Surg. 34-B:266-274 (May) 1952.

3. Fanconi, G.: Beiträge zur Nierenpathologie, Acta paediat. 40:409-431 (Sept.) 1951.

4. Klemperer, G.: Über regulatorische Glykosurie und renalen Diabetes, Berl. klin. Wchnschr. 33:571, 1896.

5. Lépine, R.: Récents travaux sur la pathogénie des diabètes, Rev. méd. Paris 16:594-599, 1896.

6. Bönniger, M.: Beitrag zur Frage des Nierendiabetes, Deutsche med. Wchnschr. 34: 780-783 (April) 1908.

7. Marble, A.; Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: VII. Non-Diabetic Glycosuria, Am. J. M. Sc. 197:533-556 (April) 1939.

8. Hjärne, U.: A Study of Orthoglycaemic Glycosuria with Particular Reference to Its Hereditability, Acta med. scandinav. 67:422-571, 1927.

9. Babson, S. G.: Renal Glycosuria, J. Pediat. 17:781 (Dec.) 1940.

10. Monasterio, G.: Histologischer und physio-pathologischer Beitrag zur Pathogenese des Diabetes renalis, Klin. Wchnschr. 18:538-541 (April 15) 1939.

11. Friedman, M.; Selzer, A.; Sugarman, J., and Sokolow, M.: The Renal Blood Flow, Glomerural Filtration Rate and Degree of Tubular Reabsorption of Glucose in Renal Glycosuria, Am. J. M. Sc. 204:22-29 (July) 1942.

12. Marble, A.: Renal Glycosuria, Am. J. M. Sc. 183:811-827 (June) 1932.

13. Albright, F.; Butler, A. M., and Bloomberg, E.: Rickets Resistant to Vitamin D Therapy, Am. J. Dis. Child. 54:529-547 (Sept.) 1937.

14. Pedersen, H. E., and McCarroll, H. R.: Vitamin-Resistant Rickets, J. Bone & Joint Surg. 33-A:203-220 (Jan.) 1951.

15. Freeman, S., and Dunsky, I.: Resistant Rickets, Am. J. Dis. Child. 79:409-427 (March) 1950.

16. Fanconi, G., and Girardet, P.: Familiärer persistierender Phosphatdiabetes mit D-vitamin-resistenter Rachitis, Helvet. paediat. acta. 7:14-41, 1952.

17. Cooke, W. T.; Barclay, J. A.; Govan, A. D. T., and Nagley, L.: Osteoporosis Associated with Low Serum Phosphorus and Renal Glycosuria, Arch. Int. Med. 80:147-164 (Aug.) 1947.

18. Albright, F.; Burnett, C. H.; Smith, P. H., and Parson, W.: Pseudo-Hypoparathyroidism—Example of "Seabright-Bantam Syndrome," Endocrinology 30:922-932 (June) 1942.

19. Fanconi, G.: Der nephrotisch-glykosurische Zwergwuchs mit hypophosphatämischer Rachitis, Deutsche med. Wchnschr. 2:1169-1171 (July) 1936.

20. Fanconi, G.: Der frühinfantile nephrotisch-glykosurische Zwergwuchs mit hypophosphatämischer Rachitis, Jahrb. Kinderh. 147:299-338, 1936.

21. Clay, R. D.; Darmady, E. M., and Hawkins, M.: The Nature of the Renal Lesion in the Fanconi Syndrome, J. Path. & Bact. 65:551-558, 1953.

22. Stowers, J. M., and Dent, C. E.: Studies on the Mechanism of the Fanconi Syndrome, Quart J. Med. 16:275-290 (Oct.) 1947.

23. Harrison, H. E., and Harrison, H. C.: Experimental Production of Renal Glycosuria, Phosphaturia, and Aminoaciduria by Injection of Maleic Acid, Science 120:606-608 (Oct. 15) 1954.

24. Bickel, H., and Smellie, J. M.: Cystine Storage Disease with Amino-Aciduria: Preliminary Communication, Lancet 1:1093-1095 (May 31) 1952.

25. Salassa, R. M.; Power, M. H.; Ulrich, J. A., and Hayles, A. B.: Observations on the Metabolic Effects of Vitamin D in Fanconi's Syndrome, Proc. Staff Meet. Mayo Clin. 29: 214-224 (April) 1954.

26. Worthen, H. G., and Good, R. A.: Concept of Renal Tubular Insufficiency with Description of Three Typical Cases, in Good, R. A., and Platou, E. S.: Essays on Pediatrics in Honor of Dr. Irvine McQuarrie, Minneapolis, Lancet Publications, Inc., 1955, pp. 305-311.

27. Anderson, I. A.; Miller, A., and Kenny, A. P.: Osteomalacia and Renal Glycosuria in Adults: Metabolic Investigation of Case with Particular Reference to Its Relation to Fanconi Syndrome and to Treatment, Quart. J. Med. 21:33-60 (Jan.) 1952.

28. Jonxis, J. H. P., and Huisman, T. H. J.: Amino-Aciduria in Rachitic Children, Lancet 2:428-431 (Aug. 29) 1953.

29. Fanconi, G.: Die tubuläre Insuffizienz und verwandte Störungen. Med. Klin. 49:209-215 (Feb.) 1954.

30. Fanconi, G.; Hanhart, E.; von Albertini, A.; Uhlinger, E.; Dolivo, G., and Prader, A.: Die familiäre juvenile Nephronophthise (die idiopathische parenchymatöse Schrumpfniere), Helvet. paediat. acta. 6:1-49 (Feb.) 1951.

31. Lightwood, R.; Maclagan, N. F., and Williams, J. G.: Persistent Acidosis in Infant, Proc. Roy. Soc. Med. 29:1431-1433, 1936.

32. Albright, F.; Consolazio, W. V.; Coombs, F. S.; Sulkowitch, H. W., and Talbott, J. H.: Metabolic Studies and Therapy in Case of Nephrocalcinosis with Rickets and Dwarfism, Bull. Johns Hopkins Hosp. 66:7-33, 1940.

33. Lightwood, R.; Payne, W. W., and Black, J. A.: Infantile Renal Acidosis, Pediatrics 12:628-644 (Dec.) 1953.

34. Schreiner, G. E.; Smith, L. H., Jr., and Kyle, L. H.: Renal Hyperchloremic Acidosis: Familial Occurrence of Nephrocalcinosis with Hyperchloremia and Low Serum Bicarbonate, Am. J. Med. 15:122-129 (July) 1953.

35. Lowe, C. U.; Terrey, M., and MacLachlan, E. A.: Organic-Acidura, Decreased Renal Ammonia Production, Hydrophthalmos, and Mental Retardation: Clinical Entity, A. M. A. Am. J. Dis. Child. 83:164-184, 1952.

36. Veil, W. H.: Physiologie und Pathologie des Wasserhaushaltes, Ergebn. inn. Med. u. Kinderh. 23:648-784, 1923.

37. Haymann, K., and Fanconi, G.: Zum Chemismus des Diabetes insipidus, Ztsch. ges. exper. Med. 51:588-598, 1926.

38. Waring, A. J.; Kajdi, L., and Tappan, V.: Society Transactions: A Congenital Defect of Water Metabolism, Am. J. Dis. Child. 69:323-324 (May) 1945.

39. Williams, R. H., and Henry, C.: Nephrogenic Diabetes Insipidus Transmitted by Females and Appearing During Infancy in Males, Ann. Int. Med. 27:84-95 (July) 1947.

40. Dancis, J.; Birmingham, J. R., and Leslie, S. H.: Congenital Diabetes Insipidus Resistant to Treatment with Pitressin, Am. J. Dis. Child. 75:316-328 (March) 1948.

41. Macdonald, W. B.: Congenital Pitressin Resistant Diabetes Insipidus of Renal Origin, Pediatrics 15:298-311 (March) 1955.

42. West, J. R., and Kramer, J. G.: Nephrogenic Diabetes Insipidus, Pediatrics 15:424-432 (April) 1955.

43. Hickey, R. C., and Hare, K.: The Renal Excretion of Chloride and Water in Diabetes Insipidus, J. Clin. Invest. 23:768-775 (Sept.) 1944.

Renal Function in Children with Leukemia

A Clinical and Pathological Study

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Although many authors* have commented on the frequency of parenchymal infiltration of the kidneys in leukemia, there has to date been no systematic study of kidney function during the course of the disease. The purpose of this paper is to present the results of the investigation of renal function in 35 patients with leukemia in the pediatric age group who have been studied during a two-year period, 1954-1955, inclusive.

Clinical results were supplemented by the pathological findings in 14 of the 35 patients who came to postmortem examination.

Methods

Blood urea nitrogen determinations, urinary specific gravity, and routine urinalyses were performed on 35 patients in whom a definite diagnosis of leukemia was established, both by bone marrow and peripheral blood examinations. The blood urea nitrogen was performed by a spectrophotometric method using glycerol urease.[7] By this method values from 10 to 16 mg/100 ml. are considered within the range of normal. Urinalyses included a semiquantitative albumin determination using the sulfosalicylic acid test with Exton's reagent, and using prepared standards for comparison.[8] A sediment formed by centrifugation was spread on a microscopic slide and examined for cellular and formed elements. The concentrating ability of the kidney was determined by the urinary specific gravity taken on early morning specimens, or after a two-hour fluid deprivation period.

Determinations were made during the following periods:

1. At the time of diagnosis and before the institution of therapy.
2. After treatment had been initiated and improvement had become evident.
3. When the patient was in remission.
4. When there was any progression of the disease.
5. At regular intervals throughout the course of the disease.
6. During the terminal period of illness.

Urea clearance studies were performed on four patients. The more sensitive measurements of kidney function by the use of intravenous renal clearance studies for the determination of glomerular filtration rate and tubular excretion were not included.

Results

The types of leukemia encountered in the 35 patients were as follows: acute lymphocytic 28; chronic lymphocytic 1; acute myelocytic 3; chronic myelocytic 3.

Renal Function Studies.—A total of 154 separate determinations of the blood urea nitrogen were performed. The results (Table 1) indicate that in 13 patients the blood urea nitrogen rose above 16 mg/100 ml. The highest value was 32 mg/100 ml. and was obtained in a patient with acute lymphocytic leukemia who was in relapse. The blood urea nitrogen, while principally dependent on the glomerular filtration rate and thus recording kidney function, is none the less dependent on protein intake and tissue destruction, that is, products of hemoglobin and white blood cell resorption. There is no reason to believe in our patients that protein intake was increased, and terminally it was probably considerably reduced. With respect to tissue destruction we have followed in five patients the serum uric acid (indicating white blood cell destruction) and in all cases the indirect serum bilirubin (indicating hemoglobin re-

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* References 1-6.

TABLE 1.—*Results of Blood Urea Nitrogen Determinations and Urinalysis Obtained in Thirty-Five Children with Leukemia*

Patient Number	Race Sex	Age at Onset	Diagnosis	Status	Duration of Disease	No. of BUN Determinations	Range of BUN, Mg/100 Ml.	Average BUN, Mg/100 Ml.	Urinalysis		
									Specific Gravity	Albumin, Mg/100 Ml.	Presence of RBC's in Urinary Sediment per High Power Field
1	W/F	11 mo.	Acute lymphocytic leukemia	Dead	11 mo.	8	7.4-20	12.2	1.010-1.034	30	Rare
2	W/F	2½ yr.	Acute lymphocytic leukemia	Dead	9 mo.	4	9.7-14.5	13.0	Not determined	Not determined	Gross blood, terminally
3	W/M	5 yr.	Acute lymphocytic leukemia	Living	3-9/12 yr.	17	10-30	13.2	1.018-1.024	5	0
4	C/M	4½ yr.	Acute lymphocytic leukemia	Living	10 mo.	9	7-15	11.1	1.010-1.020	0	0
5	W/M	6 yr.	Acute lymphocytic leukemia	Dead	10 mo.	11	8-20	13.2	1.012-1.015	Not determined	Gross blood, terminally
6	W/F	3 yr.	Acute lymphocytic leukemia	Dead	9 mo.	10	7-20	12.1	1.012-1.017	75 Terminal	Gross blood, terminally
7	C/M	7½ yr.	Acute lymphocytic leukemia	Dead	7 mo.	8	7-12	9.7	1.010-1.015	200 Terminal	Gross blood, terminally
8	W/M	2 yr.	Acute lymphocytic leukemia	Dead	14 mo.	8	7-18.5	12.7	1.022	0	0
9	W/M	4 yr.	Acute lymphocytic leukemia	Living	7 mo.	3	9-13.5	11.7	1.012	0	0
10	W/F	3½ yr.	Acute lymphocytic leukemia	Living	7 mo.	6	7.5-15.0	10.9	1.018-1.021	0	0
11	W/F	8 mo.	Acute lymphocytic leukemia	Dead	20 days	1	14.0	14.0	Not determined	Not determined	Not determined
12	W/M	16 mo.	Acute lymphocytic leukemia	Living	4 mo.	4	8-13.0	11.2	Not determined	0	0
13	W/F	5 mo.	Acute lymphocytic leukemia	Dead	3 mo.	4	7-30	15.2	1.012	320 Terminal	20-25 initially gross blood, terminally
14	W/M	16 mo.	Acute lymphocytic leukemia	Dead	6 mo.	2	12.5-14	13.2	Not determined	Not determined	Gross blood, terminally
15	W/M	6 mo.	Acute lymphocytic leukemia	Dead	21 mo.	1	13.0	13.0	1.010-1.022	10	5-10 initially
16	W/M	2½ yr.	Acute lymphocytic leukemia	Dead	Over 9 mo.	3	10.0-20.0	14.3	1.012-1.021	0	0
17	C/F	5 yr.	Acute lymphocytic leukemia	Dead	7 mo.	3	20.0-21.0	20.3	1.010-1.017	0	0
18	W/M	7 yr.	Acute lymphocytic leukemia	Dead	12 mo.	4	4.0-16.0	10.0	1.010-1.025	0	2-4

TABLE 1.—*Results of Blood Urea Nitrogen Determinations and Urinalysis Obtained in Thirty-Five Children with Leukemia*—Continued

Patient Number	Race Sex	Age at Onset	Diagnosis	Status	Duration of Disease	No. of BUN Determinations	Range of BUN, Mg/100 Ml.	Average BUN, Mg/100 Ml.	Urinalysis		
									Specific Gravity	Albumin, Mg/100 Ml.	Presence of RBC's in Urinary Sediment per High Power Field
19	W/F	4 yr.	Acute lymphocytic leukemia	Dead	10 mo.	1	15.0	15.0	1.021	0	0
20	W/F	3 mo.	Acute lymphocytic leukemia	Dead	2 mo.	1	22.0	22.0	1.012-1.017	0	0
21	W/M	4 yr.	Acute lymphocytic leukemia	Dead	12 mo.	1	18.0	18.0	1.014-1.020	20	0
22	C/M	18 mo.	Acute lymphocytic leukemia	?	Over 3 mo.	1	14.0	14.0	1.022-1.033	0	0
23	C/F	9 yr.	Acute leucosarcoma	Dead	1 mo.	1	12.0	12.0	1.015-1.026	Trace	0
24	C/F	20 mo.	Acute lymphocytic leukemia	Dead	18 mo.	1	9.0	9.0	1.013-1.026	0	0
25	W/F	2 yr.	Acute lymphocytic leukemia	Dead	21 mo.	1	15.0	15.0	1.012-1.018	45 Terminal	0
26	W/M	11 mo.	Acute lymphocytic leukemia	Dead	5 mo.	1	13.0	13.0	Not determined	0	0-1
27	W/M	2 yr.	Chronic lymphocytic leukemia	Dead	2 yr.	5	7.0-20.0	11.4	1.013	8	0
28	C/M	5 mo.	Acute myelocytic leukemia	Dead	8 days	2	8.0-11.0	9.5	Not determined	Trace	0
29	W/M	10 yr.	Acute myelocytic leukemia	Dead	2 mo.	3	7.0-9.5	8.2	1.024-1.029	30 Terminally	5 Gross blood, terminally
30	W/M	18 mo.	Acute myelocytic leukemia	Living	3 mo.	4	7.0-12.0	9.9	1.020-1.020	0	0
31	W/M	8 yr.	Chronic myelocytic leukemia	Dead	5 yr.	10	8.0-16.0	12.1	1.012-1.024	500 Terminally	Gross blood, terminally
32	W/M	13 mo.	Chronic myelocytic leukemia	Living	3½ yr.	4	12.5-19.0	14.4	Not determined	20	0
33	C/F	8 yr.	Chronic myelocytic leukemia	Living	12 mo.	2	11.0-12.0	11.5	1.010-1.017	0	0
34	C/F	9 yr.	Acute leucosarcoma	Dead	1 mo.	--	----	--	1.015-1.026	0	0
35	W/M	9 yr.	Acute lymphocytic leukemia	Living	2 yr.	10	8.0-32.0	14.6	1.018-1.030	0	0

sorption). When there has been a rapid fall in the white blood cell count, the serum uric acid has invariably been elevated; the indirect serum bilirubin has been within normal limits in all patients.

According to the observations made during the course of leukemia the renal concentrating ability (Table 1) was not demonstrated to be impaired as shown by the urinary specific gravity test. In no patient was the specific gravity less than 1.010 following a two-hour fluid-deprivation period.

Routine urinalyses (Table 1) showed an albuminuria above 50 mg/100 ml. in four patients, three of whom had acute lymphocytic and one chronic myelocytic leukemia. These patients were in the terminal phase of the disease and showed gross and microscopic evidence of leukemic infiltration of the kidneys at autopsy. No significant albuminuria (50 mg/100 ml. or more) was noted other than in specimens which were grossly bloody. Two patients at the onset of the disease showed red blood cells (Table 1) in the urine in excess of five cells per high power field. The platelet count was less than 10,000 per cubic millimeter at the time of these urine examinations. Grossly bloody urine occurred a few days prior to death in eight patients. Of these eight patients six came to autopsy, and all showed gross and microscopic evidence of leukemic infiltration and hemorrhage into the renal parenchyma.

Urea clearance tests (Table 2) were performed on four patients, two of whom (patients 4 and 35) showed elevated blood urea nitrogen values at the time of the test. The results indicate that the urea clearance was not below 90% of normal in these four patients.

Pathological Findings.—The gross and microscopic appearance of the kidneys in the 14 autopsied cases of leukemia under investigation are presented in Table 3. The kidneys showed leukemic infiltration in 13 cases. Despite marked parenchymal destruction observed at autopsy, no gross impairment in renal function was apparent as determined by the methods employed, as previously mentioned.

The kidneys were slightly enlarged in all cases, often as much as two or three times the normal size. Adherence of the capsules to the renal parenchyma was not observed. The external surfaces of the kidneys were pinkish gray and frequently showed mottled red areas as a consequence of hemorrhage. The cut surfaces of the kidneys showed, in most cases, areas of hemorrhage and loss of distinct demarcation between cortex and medulla. Microscopically, the leukemic infiltration was most evident in the cortex where there was compression, distortion, and separation of the tubules by leukemic cells. The glomeruli occasionally showed increased cellularity, and sometimes there was evidence of tubular degeneration. Areas of extravasation of blood and foci of necrosis were consistently found in the cortex and medulla as well as in the calices and pelves.

Comment

A review of the literature in which all reports concern adult patients, indicates a diversity of opinion as to whether renal insufficiency occurs during the course of leukemia. For example, Allen [9] states that at no time during the disease is there impair-

TABLE 2.—*A Comparison of Urea Clearance and Blood Urea Nitrogen Determinations*

Patient Number*	Stage of Disease	Blood Urea Nitrogen, Mg/100 Ml.	Per Cent Urea Clearance
3	Relapse	20	93
4	Terminal	14	95
10	Remission	11	97
35	Relapse	32	90

*Patient numbers identical with Table 1.

ment of kidney function, while Wintrobe [10] alleges that in advanced cases the clinical picture resembles that of uremia.

Locke and Minot [2] observed hematuria in 15% of 110 patients with chronic myelocytic leukemia. Hematuria occurred in 20% of 80 patients with chronic lymphocytic leukemia, in 8% of whom it was marked and associated with intense pain and enlargement of the abdominal lymph nodes.

TABLE 3.—*The Correlation of Clinical and Pathological Findings in Fourteen Autopsied Cases of Leukemia*

Pathological Examinations of Kidneys

Patient Number*	Therapy	Gross	Microscopic
1	6-Mercaptopurine; steroids	Wt. 2×normal; soft, light pink; poor corticomedullary demarcation; pelves and calices filled with blood clot	Leukemic infiltration into perirenal tissue and capsule; increased cellularity of glomeruli; leukemic infiltration around glomeruli and tubules with compression and distortion of tubules
2	4-Aminomethylpteroylglutamic acid (A-methopterin); 6-mercaptopurine; steroids	Wt. slightly increased over the normal; purplish-gray hemorrhages in cortices	Interstitial infiltration with leukemic cells; one large area of hemorrhage
5	6-Mercaptopurine; steroids; azaserine; triethylene melamine	Wt. 2×normal; surfaces studded with petechial hemorrhages; kidneys soft and flabby and purplish gray; poor corticomedullary demarcation; cortices contained numerous hemorrhagic areas; pyramids congested	Leukemic infiltration into perirenal tissues and capsule; increased cellularity of glomeruli; leukemic infiltration around glomeruli and tubules with tubular separation and degenerative changes; areas of hemorrhage and necrosis
6	6-Mercaptopurine; steroids; 4-aminomethylpteroylglutamic acid	Wt. 3.5×normal; subcapsular hemorrhages; large, soft and yellowish pink; hemorrhagic areas throughout cortex and medulla; calices and pelves filled with blood	Leukemic infiltration into glomeruli and throughout entire parenchyma; compression and distortion and degenerative changes of tubules; areas of hemorrhage and necrosis
7	6-Mercaptopurine; steroids; irradiation	Wt. 2×normal. Hemorrhagic areas over surfaces; on section pelves dilated and filled with blood clot; poor corticomedullary demarcation	Hemorrhage and leukemic infiltration into perirenal tissues and capsule; increased cellularity of glomeruli; leukemic infiltration around glomeruli and tubules, most marked in cortex; early degenerative changes of tubules; large areas of hemorrhage and necrosis
8	6-Mercaptopurine; steroids	Wt. slightly increased over normal; pale pink; poor corticomedullary demarcation	Marked congestion of pyramids; no leukemic infiltration
13	6-Mercaptopurine; steroids	Wt. 2×normal; soft and pinkish; poor corticomedullary demarcation; subcapsular petechial hemorrhages	Increased cellularity of glomeruli; small areas of leukemic infiltration around glomeruli and tubules
14	6-Mercaptopurine; steroids	Wt. slightly increased; capsules strip easily; surfaces studded with pinkish-gray areas; poor corticomedullary demarcation	Leukemic infiltration around glomeruli and tubules; small areas of necrosis and hemorrhage in cortex; hyaline changes in tubules
18	Cortisone; corticotropin (ACTH); 6-mercaptopurine; 4-aminomethylpteroylglutamic acid	Wt. 2×normal; large, pale pink subcapsular petechiae; corticomedullary degeneration indistinct; diffuse cortical petechiae	Extensive interstitial leukemic infiltration, most marked in cortices compressing glomeruli and tubules; degenerative changes of tubules
20	Cortisone; corticotropin	Wt. 1.5×normal; firm, smooth, reddish purple; cortical congestion	Glomerular tufts compressed and congested; subcapsular spaces widened; tubular degeneration and and dilation; several areas of leukemic infiltration; area of hemorrhage
24	4-aminomethylpteroylglutamic acid; steroids; azaserine; 6-mercaptopurine; chloropurine	Wt. 2×normal; large, firm, smooth, and reddish purple.	Marked tubular degeneration and foci of leukemic infiltration
25	Corticotropin; cortisone; 6-mercaptopurine; 4-aminomethylpteroylglutamic acid	Wt. 2×normal; large, firm, smooth, and pinkish purple; poor differentiation between cortex and medulla	Leukemic infiltration around glomeruli; a few glomerular tufts degenerated; tubules slightly dilated and slight to moderate cellular degeneration
28	Steroids	Wt. 3×normal; surfaces pinkish yellow and studded with small petechiae; poor differentiation between cortex and medulla	Glomeruli infiltrated with leukemic cells; extensive leukemic infiltration into the interstitial tissue; tubular degeneration; blood vessels distended with leukemic cells
34	Triethylene melamine	Wt. slightly greater than normal; light brownish-purple cortex and medulla poorly demarcated	Dense and diffuse leukemic infiltration throughout parenchyma, more marked in the region of arcuate and lobular arteries

* Patient numbers identical with Table 1.

The authors explained the hematuria in some cases by the presence of thrombocytopenia and in others by leukemic infiltration of the kidney or enlargement of the neighboring lymph nodes producing venous engorgement of the organs. In our series of patients gross hematuria was present only during the terminal phase of the disease and occurred in the presence of marked thrombocytopenia.

Clerc † has reported a patient with leukemia showing an albuminuria of 2 gm. in 24 hours. In a few instances of leukemia, Bence-Jones proteinuria has been observed.[11]

Rosenstern ‡ studied urinary sediments and found an excess of uric acid and leukemic cells in patients undergoing treatment with x-rays.

According to Bell [12] rare cases of leukemia die of uremia, and in such instances at autopsy very large kidneys are found with massive leukemic infiltration. The renal insufficiency in such cases is due to the great reduction in functional renal parenchyma. Merrill and Jackson [13] found in 18 autopsied patients, 10 instances of impaired renal function prior to death. Of these four died in uremia. All of these authors' patients were adults. The instances of patients 3 and 35 could be inferred to imply that although the blood urea nitrogen was occasionally elevated to 20-32 mg/100 ml. the urea clearance was normal. Such slight deviations may be due to absorption and disintegration of large amounts of protein, releasing nitrogen into the nitrogen pool and thus increasing the urea levels of the blood.

It has been well established that the blood uric acid frequently increases in leukemia.§ This is probably a reflection of the excessive production of uric acid resulting from the disintegration of large numbers of fragile and immature cells which produces an increase in nucleic acid and purine metabolism.

With the advent of potent therapeutic agents capable of producing rapid and extensive nuclear destruction, there have been occasional reports of uremia following this therapy in patients with leukemia and lymphoma. In those patients urinary obstruction resulted from the precipitation of urates and uric acid in the collecting tubules or ureters. There have been 17 such cases of uremia reported thus far, either following the use of chemotherapeutic agents or x-ray therapy.‖ Only one of these cases, however, occurred in a child while being treated for Hodgkin's disease [20] with triethylene melamine. Uremia did not occur except in the presence of obstructive uropathy.

Gowdey and Neuhauser [25] in a study of intravenous pyelography in children with leukemia found that iodopyracet (Diodrast) clearance by the renal tubules was well preserved. Despite this fact, roentgenographic changes indicative of leukemic infiltration were present.

Despite the varied and occasionally conflicting reports in the literature of renal function in leukemia, it seems apparent from the present study that in the pediatric age group there is no gross detectable impairment of renal function during the course of the disease. One would expect to find less evidence of renal impairment in a child with leukemia who had suffered no kidney damage prior to the development of leukemia than in the adult patient with possible preexisting renal damage and subsequent leukemic involvement. This would be substantiated by a comparison of the present results with those of previous authors ¶ who have studied the disease in adult patients.

The significant observation of this study is that, despite the presence of gross and microscopic leukemic infiltration of the kidneys and the frequent terminal finding of blood in the urine, the renal tests employed

† Clerc, cited by Mach, R. S.*

‡ Rosenstern, cited by Mach, R. S.*

§ References 14-18.

‖ References 13, 19-24.

¶ References 12, 13, 19, 21-24.

revealed no impairment of the function of this organ.

Summary

In a group of 35 children with leukemia results of kidney function studies are presented. These renal tests included urinalyses, blood urea nitrogen and urea clearance determinations.

The gross and microscopic pathology of the kidneys in 14 of these patients is correlated with the respective renal function data.

From the findings reported it can be concluded that there is no evident impairment of renal function during the course of leukemia despite the fact that postmortem examination reveals the presence of gross and microscopic infiltration of the kidney parenchyma.

REFERENCES

1. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Springer-Verlag, 1923, p. 587.

2. Locke, E. A., and Minot, G. R.: Hematuria as a Symptom of Systemic Disease, J. A. M. A. 83:1311, 1924.

3. Forkner, C. E.: Leukemia and Allied Disorders, New York, The Macmillan Company, 1938, p. 350.

4. Chute, R.: Malignant Lymphoma and the Urinary Tract, J. A. M. A. 97:969, 1931.

5. Barney, J. D.: Lymphoblastoma as Seen by a Urologist, New England J. Med. 205: 1038, 1931.

6. Mach, R. S.: Le syndrome urinaire dans les leucémies, Red. méd. Suisse Rom. 51:35, 1931.

7. Fister, H. J.: Manual of Standardized Procedures for Spectrophotometric Chemistry, New York, Standard Scientific Supply Corporation, 1950.

8. Bray, W. E.: Clinical Laboratory Methods, Ed. 4, St. Louis, C. B. Mosby Company, 1951, p. 44.

9. Allen, A. C.: The Kidney: Medical and Surgical Diseases, New York, Grune & Stratton, Inc., 1951, p. 545.

10. Wintrobe, M. M.: Clinical Hematology, Ed. 3, Philadelphia, Lea & Febiger, 1951, p. 852.

11. Boggs, T. R., and Guthrie, C. G.: Bence-Jones Proteinuria in Leukemia, Bull. Johns Hopkins Hosp. 24:368, 1913.

12. Bell, E. T.: Renal Diseases, Philadelphia, Lea & Febiger, 1946, p. 309.

13. Merrill, D., and Jackson, H., Jr.: The Renal Complications of Leukemia, New England J. Med. 228:271, 1943.

14. Cantarow, A., and Trumper, M.: Clinical Biochemistry, Ed. 5, Philadelphia, W. B. Saunders Company, 1955, p. 201.

15. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry Interpretations, Baltimore, Williams & Wilkins Company, 1946, Vol. 1.

16. Martin, C. L., and Denis, W.: A Chemical Study of Blood Changes Following Roentgen Ray Treatment of Leukemia, Am. J. Med. Sci. 160:223, 1920.

17. Jugenburg, A., and Tschotschia, K.: Neue Ergebnisse zum Verständnis des Leukämieverlaufes, Strahlentherapie 41:86, 1931.

18. Sandberg, A. A.; Cartwright, G. E., and Wintrobe, M. M.: Studies on Leukemia: 1. Uric Acid Excretion, Blood 11:154, 1956.

19. Weisberger, A. S., and Persky, L.: Renal Calculi and Uremia as Complications of Lymphoma, Am. J. M. Sc. 225:669, 1953.

20. Merrill, D.: Uremia Following X-Ray Therapy in Leukemia, New England J. Med. 222:94, 1940.

21. Kravitz, S. C.; Diamond, H. D., and Craver, L. F.: The Clinical Use of Triethylene Melamine, Blood 7:729, 1952.

22. Kravitz, S. C.; Diamond, H. D., and Craver, L. F.: Uremia Complicating Leukemia Chemotherapy: Report of a Case Treated with Triethylene Melamine, J. A. M. A. 146:1595, 1951.

23. Bedrna, J., and Polcák, J.: Akuter Harnleiterverschluss nach Bestrahlung chronischer Leukämien mit Röntgenstrahlen, Med. Klin. 25: 1700, 1929.

24. Lear, H., and Oppenheimer, G. D.: Anuria Following Radiation Therapy in Leukemia, J. A. M. A. 143:806, 1950.

25. Gowdey, J. F., and Neuhauser, E. B. D.: The Roentgen Diagnosis of Diffuse Leukemic Infiltration of the Kidneys in Children, Am. J. Roentgenol. 60:13, 1948.

The Child's Emotional Response to Hospitalization

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It is generally agreed that it is more difficult for human beings to face the unknown than the known. The child entering the hospital, especially for the first time, is facing the unknown, and his anxiety in this situation may be extreme. This paper is concerned with the role of the physician in minimizing this anxiety as he prepares his patients for hospitalization and supervises the child's care in the hospital.

Over the past 20 years many studies have been conducted to determine the emotional effects of hospitalization on the child.* Observations have been made of significant changes in the behavior of the child which were not present before hospitalization, the duration of such changed behavior, and the age groups in which it has occurred. It was found that 20% of the hospitalized children showed the following significant behavior changes after hospitalization (in one study this figure reached as high as 50%)[4]: regressive behavior, with extremely increased dependence, loss of bowel or urinary control, loss in the ability of self-help; fears—excessive fears of hospitals, white coats, darkness, strangers, bodily harm; sleep disturbances—night terrors, difficulty in going to sleep; speech disturbances—voice changes, refusal to talk; eating disturbances; tics and mannerisms; negativistic reactions—disobedience, temper tantrums, defiance, destructive behavior.

The change in behavior ranged in duration from several months to three or four years. Approximately 50% of these children were under the age of 4 years at the time of hospitalization. From these studies,† it was concluded that emotional trauma in the hospital experience may be prevented by (*a*) an adequate parent-child relationship; (*b*) proper preparation of both the parent and the child for the experience of admission, hospitalization, and discharge, and (*c*) modifying the hospital experience as much as possible to meet the endurance of the child and his parents.

Modern pediatric training stresses the importance of the physician in helping parents build an adequate parent-child relationship. This point, however, is not within the scope of this paper. We are concerned here with what we as physicians can do about the preparation of the child for hospitalization and about modifying the hospital experience to meet the needs of the child and of his parents, as well as our own.

The staff of the Pediatric Mental Health Unit at the University of California Medical Center has, for the past several years, conducted a study of the reactions of children and their parents on the child's admission to this hospital and during his hospital stay, to determine what might be useful for physicians to know in caring for hospitalized children. For our presentation, the reactions of the child and of his parents will be considered separately, although it is apparent that the reactions of both are closely interwoven and highly synergistic.

Method

It was of interest to us to hear what the children themselves had to say about their hospital experience. Therefore, we interviewed 100 of these

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* References 1-4.

† References 1, 2, and 4.

children in the age range of 3 to 15 years and told them that we, as members of the pediatric staff, were interested in what they thought about being in the hospital. The following questions were asked of each child while he was in the hospital:

1. What did mother or father say was the reason you were brought to this hospital?

2. What do you think is the matter with you?

3. What have the doctors and nurses done so far?

4. Do you know what else they are going to do before you go home?

Their responses to these questions brought up, in turn, the points which we discuss in this paper:

I. How well or how poorly children themselves are prepared for hospitalization.

II. How much children can understand about illness and whether this understanding is useful to them.

III. What children have to say about hospital routine and our care.

I. How Well Are Children Themselves Prepared for Hospitalization?

The responses of the children regarding their preparation for hospitalization are distributed as shown in the Table. It is apparent from the Table that only 25% of the children, as judged by their responses, had been adequately prepared for hospitalization.

Examples from the four response categories are presented for clarification. Of the 26 whose parents had not prepared them in any way for hospitalization, the following replies were typical:

A 3-year-old, chewing tearfully on a doll blanket, answered to our first question: "To go home tomorrow. She said she'd bring a toy."

"Why are you here now?"

"She didn't let me go home."

A 6-year-old, in response to questioning, said: "Don't know. My doctor said I didn't have to, but this other thing, he said I had to, and mother said 'yes'."

This child was one of the most difficult for the staff to manage, in terms of cooperation for procedures and treatment. His lack of preparation may have been a large factor in this difficulty.

An 11-year-old said: "She never told me. I guess 'cause I'm sick, so I can get better. Hard to remember. I don't think she did tell me, though."

The next group are from the 22 children whose parents had prepared them by giving them a vague reason:

A 3-year-old said: "To be fixed up." He was, however, unable to say what was to be fixed.

A 6-year-old answered: "To get me well." He, too, was unable to elucidate further.

A 7½-year-old replied: "To be checked."

"For what?"

"I don't know. She said to be examined."

The following examples are from the 27 children whose only preparation had been overhearing symptoms or diagnoses, which further questioning revealed they did not understand:

A 5-year-old girl with rickets said: "They're going to check me because I'm bowlegged."

"What does 'bowlegged' mean?"

"I don't know. I heard my mother say it."

A 7-year-old girl, when asked what she thought was the matter, answered: "I have protein in my urine."

"What does this mean?"

"I don't know; I heard my daddy say it."

Many children were sick because of "glands," but had no idea what glands were. When explanations were not given or were not within the children's understanding, they seemed to conjure up their own.

A 10½-year-old boy with possible rheumatic fever informed us that his spleen had been removed on previous hospitalization.

"What is a spleen?"

Preparation of Children for Hospitalization

No. of Children	Preparation as Judged by Response	Age Range This Group, Yr.	Age Range Greatest %, Yr.
26	No preparation	3-13	4-6
22	By vague reason	3-13	6-9
27	By giving or overhearing diagnosis or symptoms	3-13	5-8
25	By giving good understanding of illness (25% of this group were 4-6 yr.)	4-15	11-15

"A big, round thing that grows pipes; luckily mine didn't. A friend of mine's did, and they didn't get the pipes out and he died."

"What do you mean by pipes?"

"I don't know."

An even more confused explanation was given by a 6-year-old boy in the hospital for fever of undetermined origin. He said he was here to find out why his head hurt.

"Why do you think it hurts?"

"Mother thinks I got wool in my lungs from an old blanket. I passed some of it up through my nose. My x-rays show a black covering over my lungs, but I think it was from a fall.

The above responses illustrate the confusion and difficulties of the child who enters the hospital with little or no idea of why he is there or with little understanding of his illness. If good preparation for hospitalization is necessary, the question is then raised: Can the reason for hospitalization and a simple explanation of his illness be understood by the child? Some illustrative responses from the children who were well prepared may answer this question.

II. How Much Can a Child Understand About Illness, and Is This Understanding Useful to Him?

Only 25 of the 100 children were able to give a good explanation of why they were in the hospital and used medical terms which they understood. This group showed that children are able to understand when explanations are given to them in simple terms. For example:

A 10-year-old boy defined rheumatic fever as: "Your heart is tired and needs a rest."

A 9-year-old girl with hypothyroidism said she had a thyroid deficiency.

"What does this mean?"

"I have no thyroid gland. A thyroid gland helps your food go all over your body, to grow, and if you don't take pills, you gain weight. I will have to take pills all my life."

An 11-year-old boy gave quite a lecture on nephritis, or, as he said: "I have 'nethritis' in my kidneys, and I'm here for tests on me and to rest more."

"What do you mean 'nethritis' in your kidneys?"

"It means your kidneys are infected."

"Infected?"

"Your urine gets pus and blood. It's not bad now, but if I walk around it will get worse and then they can't stop it."

"Are you worried about that?"

"I'm not a bit worried. I know they will make me better, and if I stay in bed, I can't get any worse. Since I've been here, they've taken blood tests. They had to do it 13 times to get blood 9 times. It didn't feel good, but if it shows I'm getting better, I'll never miss it."

A 4-year-old girl, seen prior to a tonsilloadenectomy, said: "They are going to take my tonsils out."

"Where are they?"

"In the back of my throat, and they're going to take out something else back of my nose. I have to stay one and a half to two days."

These samples show that even a 4-year-old child can be prepared for hospitalization and the necessary procedures, if explanations are given in simple terms. It is evident from the comments of the older boy and girl how important is the element of the child's understanding of his illness in relation to his cooperation with procedures and in his follow-through on future care.

III. What Do Children Have to Say About Hospital Routine and Our Care?

The remarks of the children themselves are important in these considerations. They were usually elicited by the last two questions: "What have the doctors done so far?" and "What else are they going to do before you go home?"

First, let us consider the process of admission. Since it involves separation from the parents, admission is perhaps the most traumatic experience of hospitalization for a child as well as the parent because both are so intimately involved. This will be discussed in more detail when the parents' reactions are considered in the hospitalization of their child.‡ We have observed that when the child and his parents have been well prepared for the hospitalization admission is less difficult than in the cases in which this preparation has not been given. It is also important to stress the role the physician and the nursing staff can play in

‡ To be published.

diminishing the anxiety which accompanies admission. This separation anxiety can be reduced by an admission procedure administered to allow for a gradual separation of the child from his parents.

Most of the children who enter a children's ward are lonely for their parents, uncomfortable in this new, strange situation, confused about why they are in the hospital, and fearful as to what is going to happen to them. The physician and nurse can help the child with these feelings, first by understanding that children usually react to stress in a variety of ways. Some, especially younger children, will express their uncomfortable feelings openly and verbally, with much crying. Others will become quiet and withdrawn—to the nurse or physician who is inexperienced with children, these children will give the impression of being well adjusted to hospitalization because they do not cause any trouble.

Some children may handle their uncomfortable feelings by becoming belligerent, bossy, or destructive and by refusing to cooperate in any way with procedures and treatments. Underneath, these children are just as frightened and lonely as those who cry and say they are frightened. This belligerent expression of their underlying fear and loneliness is the most difficult for a hospital staff to handle, because of the staff's own reactions of irritation and antagonism to such children. As Dr. E. A. Park [8] said in a speech on the opening of the new Hospital for Sick Children in Toronto:

> I can say from experience that in dealing with ignorant, prejudiced and utterly unreasonable parents and with some devil-born children it is difficult or impossible, to retain one's equanimity. I know, too, that it is altogether too easy to economize time and effort by the substitution of force for those devious ways of dealing with children which are so effective and avoid scars, that is, explanation, persuasion and distraction. But these are time consuming. A child can be altogether too easily overpowered and treated as something inanimate.

In helping our young patients with those uncomfortable feelings, which are usually expressed in one of these three ways, there is one principle on which our method should be based. It is the acceptance by the physician and nurse of the child's needs to react to stress.

Coming to the hospital, often feeling sick and in pain, being separated from his parents and familiar surroundings, and placed under the care of strangers make up one of the most difficult situations a young child has to face.[6] Yet, at the same time, he is required to submit to new and often painful procedures. If he makes much protest, the staff may scold him or at the most quiet him. As Pearson [7] says, "In the face of overwhelming terror, we often require him to be passive." Or, in our efforts to help him, we may give what seems to him false reassurance. It is common for the nurse or physician to try to reassure the child by saying there is nothing of which to be afraid or that there is no need to cry from loneliness when he is surrounded by doctors and nurses to care for him. This seldom will remove his feeling of fear or loneliness, and the child then carries the additional burden of feeling it is wrong to be afraid or lonely and to show it. Yet, one of the basic principles of child psychiatry is that if the child is encouraged and helped to express his troubled feelings to an understanding person, he is often relieved by being able to relate and communicate these feelings. The frightened, lonely hospitalized child will benefit more by a physician or nurse who recognizes the importance of helping the child to express his feelings.

Either the nurse or the physician can say that she knows how frightened the child is at being in a strange place, or at going off with a nurse and leaving his mother, but that it is all right to be frightened, that it is all right not to want to stay and to prefer to go home. But it must be added that even though the child doesn't like it, and even though the nurse or doctor does understand, nevertheless, he does have to stay and that everyone will help as much as possible.

One of our patients indicated that this sort of management would have helped her:

A 6½-year-old girl said: "I was unhappy when I had to stay. I cried, but sometimes I don't, I get real mad and hate staying. I cry and tell them I don't want to stay."

"What do they say?"

"I don't know, I really don't tell them anything about it."

"Would it help if you could?"

"Yes, it would. I came to get my cold all gone, but I hate staying."

Some past studies§ have indicated that it is common for children to interpret illness and hospitalization as punishment for misbehaving. In our own study, we did not find this interpretation to be common. However, several of the children gave some indication that they felt their illness was partly on the basis of misbehavior.

A 6-year-old boy with eczema said: "I scratched my hand and everything and my temp ran up."

"What is a 'temp'?"

"When my boy friend came in and I got too excited, my temp ran up."

Another 6-year-old boy, with dwarfing, said he was in the hospital "Because I'm not eating well. I don't get the things I like, like hamburger, weenies, and baked potatoes, not the yellow kind. My mother wants me to learn to like other things, but I can't swallow them; that's why I'm here."

A 10-year-old child with asthma described asthma as: "It's hard breathing and it's awful. I have it because I have too much energy and run around and laugh too hard and get too much house dust."

It is important for physicians to make sure that our patients do not have this interpretation of their illness and hospitalization. We may be able to correct their misinterpretations, as well as give them a better understanding of their illness, by asking them when we examine and treat them why they think they are in the hospital and what they think is causing their illness.

The child's life in the hospital should be as normal as possible. He will be happier if he is dressed and allowed to play with other children during the day. If it is necessary to restrict him to bed, or to isolate him, this should be explained to him at the level of his understanding, so that he does not interpret this as punishment. Good nursing care should include the provision of play equipment and amusements for the child. Schooling should continue, if possible, either with a teacher assigned to the ward or with frequent visits from a home teacher. The staff can also be helpful to the child by being aware that seemingly insignificant hospital routine can be very important to the young patient and may require explanation. The following are some examples:

A 6-year-old girl with convulsions contrasted this hospital with another, saying: "I had a longer bed before."

"You think this one is too small?"

"I think cribs are for babies, and I don't like this crib."

When told that she was a pretty big girl, that hospital beds are pretty far off the floor, and we wanted to be sure that she didn't roll out while she was sleeping, she accepted the crib with less distaste.

An obese, sensitive 11-year-old adolescent girl had never been away from her mother and, according to her mother, was "satisfied about coming until she was told on admission she couldn't wear her own pajamas." This girl had matured early and had quite well-developed breasts. She said she didn't feel the hospital gown would cover her well and didn't want to stay. When we saw her, she was sitting in bed in the admitting unit, flushed, hot, and unhappy, with her bathrobe on and the covers up to her neck. On inquiry, we discovered that she thought the gown tied in front, so that it was true her breasts and fat abdomen would have been quite exposed. After a demonstration of how the gown went on, she took off her robe, relaxed, and accepted admission to the hospital.

Painful procedures are difficult for the physician as well as for the patient. If the child can be helped to undergo this stressful situation with as little physical and emotional suffering as possible, the physician will feel better and will be able to manage subsequent situations with more self-assurance. Two basic principles underlie this help: (1) preparation of the child for the procedure and (2) the recognition and acceptance of his feelings about it. Every child, even a 2-year-old, should be told as simply and honestly as possible what is going to happen to him. For example:

§ References 8-10.

Recently, a 9-year-old girl was in our ward with a ruptured pancreas and pancreatic cyst on the basis of a bicycle handlebar injury. She was sent to University of California Hospital for surgery because she was absolutely uncooperative in her local hospital. She would pull out the Levin tubes and the intravenous tubes, refused to eat, and wet and soiled her bed. Here, although not one of our most cooperative patients, she did none of these things. As time went on (she was here five weeks), she became most cooperative and before discharge was a favorite of the doctors and nurses. What accounted for the changed attitude? In Sydney's words: "In the other hospital no one there liked me, they just put me in a room alone with nothing to do; they didn't care. They never told me anything—never told me what they were going to do—just started it. I didn't know what to expect ever. They told me I'd have to have the tube one day; and I thought they'd stop. After one day I pulled it out, and they didn't come back for a long time to put it back."

Here she said, it was different.

"They always told me what they were going to do beforehand; I know the doctors here meant business, and there was no use to pull out the tube."

The child should be allowed to express his feelings about any painful or frightening experience. He should be told that we understand he doesn't like it, that it is all right for him to be frightened, that we understand his feeling, but that it has to be done. It is of help to the child if the nurse can stay a little while after a procedure to let the child know she "respects the fact that he has experienced something unpleasant and give him an opportunity to express his feelings."[11]

The child in the hospital should not be exposed to children who are very sick or who are experiencing painful procedures, or be subjected to the sight of other children who have had mutilating accidents. Children, especially in the preschool age, often think that what is being done to one child in the hospital will also be done to him. In our toddlers' ward, a child was having a duodenal drainage. As he protested and cried, all the other children started to cry, and one of them indicated that he thought he was next. It is demoralizing, too, for the older child to break down under the stress of a painful procedure in the presence of others. To avoid this unnecessary emotional trauma, we feel all painful procedures should be conducted in separate treatment rooms.

Ward rounds can also be a source of anxiety for these "little pitchers with big ears." Vander Veer,[12] of the University of Chicago, says:

Pernicious is the bedside discussion conducted about the child and within his hearing, though without his participation, in a language full of strange words and reference to stranger diagnostic technics. This hoary rite, which is still practiced almost universally, may arouse great fear in the patient about what is wrong with him or what is being done to him.

A 6-year-old girl with pyelitis overheard the physicians talk about the "bugs" in her urine and urinary tract. She disclosed that she thought these bugs were something like spiders and was quite fearful in her expectation that at some time they would crawl out of her.

Discussion of the child in front of him in words he does not understand or cannot hear, should be avoided by all personnel.

A 13-year-old girl having Boeck's sarcoid with central nervous system involvement, when asked what else the doctors were going to do before she went home, said: "Exercises, and I don't know. They don't talk much about it. They come and see me and talk low and then go out, and that's the trouble, they don't tell me."

When queried whether she ever asked questions, she said: "Sometimes, but they say they don't know. I wonder if they really don't."

We do not mean to infer that this child should have had a lecture on the pathology of Boeck's sarcoid and its prognosis. These children are puzzled by the physicians who come around, look at them, and talk in low voices, without a word to them. If, instead, the physician could make a reassuring remark about the progress of the child's particular condition and then carry on the medical discussion outside the room, our patients might be more comfortable.

Children are quite observant of the examination, and if the physician seems especially interested in one aspect, they are sure something is wrong.

A 14-year-old girl had fundi with some questionable findings which were, after several examinations, found normal. She said: "Eleven doctors

have examined me and they sent me to the Eye Clinic, I don't know why. They said it was normal, but they're making so much fuss over it. Three looked at it there.

The boy mentioned before, who was passing the old blanket out through his nose, said: "They listened to my heart. The doctor said it sounded like a cannon. It scared me at first; I guess those are pretty powerful things you listen with."

Children tend to take statements of physicians and nurses very seriously, and may be quite disturbed by remarks meant to be joking or teasing.

A bright, sensitive 7-year-old girl was investigated in our ward because of precocious puberty. She had pubic and axillary hair and breast development and was menstruating. When she was asked what the doctors had done so far, she told of all the procedures, which included the taking of some photographs. "They took pictures of parts of my body—one of the doctors said it was going to be in Life Magazine."

"Did you believe that?"

"Well, I thought he was serious. I hope they don't put my name with it, and I hope my mother and father and grandparents don't see it."

(Needless to say, this worry, based on the heedless remark of a medical student, was immediately corrected by the attending physicians.)

Although an effort was made to be objective during this study, it was impossible, after the children's responses, not to modify our ward routine as we progressed. This, after all, was the most important result of this study, and these modifications will be discussed in a subsequent publication.

Conclusions

From this study of the child's emotional response to hospitalization, it was concluded that 75% of the pediatric hospital patients are not prepared for hospitalization. Most children from the age of 3 or 4 years can gain some understanding of their illness and the treatment necessary, if explanations are given in simple terms. This means that children can be adequately prepared for hospitalization if physicians will realize the importance of such preparation and make the necessary effort.

Children who receive explanations for the necessity of procedures and whose feelings are understood seem more cooperative during procedures and treatment.

Many areas in hospital routine can be modified to the increased welfare of the hospital child by (*a*) explanation of hospital routines necessary for the care and well-being of the child; (*b*) conducting painful procedures in treatment rooms separated from the observation of other children; (*c*) conducting ward rounds and examinations with an awareness of the child as an understanding individual with feelings.

The physician can play an important role in minimizing emotional trauma from hospitalization if he prepares his patient adequately for this experience and works with the hospital personnel to modify hospital routine to meet the child's needs.

REFERENCES

1. Levy, D. M.: Psychic Trauma of Operations in Children, Am. J. Dis. Child. 69:7-25 (Jan.) 1945.

2. Jessner, L., and Kaplan, S.: Observations on the Emotional Reactions of Children to Tonsillectomy and Adenoidectomy, in Problems of Infancy and Childhood, Transactions of the Third Conference, March, 1949, edited by M. Senn, New York, Josiah Macy, Jr., Foundation, 1949.

3. Jackson, K.; Winkley, R.; Faust, O. A., and Cermak, E. G.: Problem of Emotional Trauma in Hospital Treatment of Children, J. A. M. A. 149: 1536-1538 (Aug. 23) 1952.

4. Prugh, D. G.; Staub, E. M.; Sands, H. H.; Kirschbaum, R. M., and Lenihan, E. A.: A Study of the Emotional Reactions of Children and Families to Hospitalization and Illness, Am. J. Orthopsychiat. 23:70-106 (Jan.) 1953.

5. Park, E. A.: Preservation of Ideal in University Children's Clinic, Canad. M. A. J. 66:478-485 (May) 1952.

6. Maclennan, B. W.: Non-Medical Care of Chronically Ill Children in a Hospital, Lancet 2:209-210 (July 30) 1949.

7. Pearson, G. H. J.: Effect of Operative Procedures on the Emotional Life of the Child, Am. J. Dis. Child. 62:716-729 (Oct.) 1941.

8. Freud, A.: The Role of Bodily Illness in the Mental Life of Children, in the Psychoanalytic Study of Child: Vol. 7, edited by R. S. Eissler and others, New York, International Universities Press, Inc., 1952, pp. 69-81.

9. Langford, W. S.: Physical Illness and Convalescence: Their Meaning to the Child, J. Pediat. 33:242-250 (Aug.) 1948.

10. Beverly, B. I.: The Effect of Illness upon Emotional Development, J. Pediat. 8:533-543 (May) 1936.

11. Wallace, M., and Feinauer, V.: Understanding a Sick Child's Behavior, Am. J. Nursing 48:517-522 (Aug.) 1948.

12. Vander Veer, A. H.: Psychopathology of Physical Illness and Hospital Residence, Quart. J. Child Behavior 1:55-71 (Jan.) 1949.

A Follow-Up Study of Hemangiomas of the Skin Treated and Untreated

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The unsightly nature of a circumscribed reddish vascular nevus, elevated above the surface of the skin, in children, causes a great deal of distress to their parents, who, therefore, seek medical advice early in almost all cases. Some authors state that in vascular nevi of the elevated type the earlier treatment is applied after their appearance the better are the results obtained, since these lesions tend to grow with the child.* Other authors reserve treatment for special cases only, for cosmetic or functional purposes, or to prevent ulceration with secondary infection and hemorrhage.† J. Walter [8] found that radiation or other treatments can make vascular nevi disappear faster, but he concludes that, unless there are positive reasons for early treatment, this is usually unnecessary and may well be considered undesirable. Bowers,[7] in analyzing 20 successful cases treated with thorium X, came to the conclusion that at least 13 among them recovered spontaneously, without thorium X being an appreciable factor in their cure.

Since there is still no general agreement on the management of patients with this common lesion, we decided to undertake an investigation into the fate of a group of vascular nevi left untreated and compare them with a group of nevi treated by the usual radiation methods. The object of this paper is to report the results of this investigation.

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* References 1 and 2.

† References 3, 4, and 6.

Material and Methods

During a four-year period, 1945-1948, one of us (W. F.) treated 116 cases of vascular nevi. In most of these cases the parents were advised to leave the lesions to their natural course. However, in those cases where erosion and ulceration with hemorrhage or severe disfigurement of the body part were likely to occur, radium therapy was advised and carried out.

The names and addresses of all the 116 children were available. They were scattered over an area including 28 communities, and many of them changed their residence in the intervening period one or more times. Because of this, it was impossible to locate 55 of the 116 patients. The remaining 61 were traced and reexamined after a lapse of five to eight years. One of these patients was treated by a smallpox vaccination at the site of the nevus and is therefore excluded from this comparative study. The remaining 60 patients constitute the material of this investigation. Since no other factor was operative in the selection of patients except their availability for reexamination, this group of patients may be considered a random sample and therefore suitable for statistical evaluation. The pertinent data pertaining to these 60 patients are presented in Table 1.

As seen in Table 1, the age of the 60 patients at the time of their first examination ranged between 1 month and 4½ years; 14 of them were under 6 months; 31, under 1 year, and 52, under 2 years of age. There were 23 boys and 47 girls. Fifty-two of the sixty patients had a single nevus each; five patients had two nevi each; two had three nevi each, while one had four nevi. In all, there were, thus, 72 lesions. Their frequency distribution according to size is shown in Table 2, and their distribution according to their location on the body is shown in Table 3.

Of the 72 lesions available for reexamination, 14 had been treated with radium. Four among the radiated nevi were so treated because of their localization (lips, nose, eyelid), while the rest were treated because of pressure applied by overzealous relatives.

The ultimate fate of each lesion was determined at the reexamination of the patients. The final

TABLE 1.—*Clinical Data of Sixty Patients with Hemangiomas*

Case	Age when First Examined, Mo.	Sex	Nevi, No.	Location	Largest Diameter, Mm.	Management		Outcome of Management at Reexamination			
						Conservative	Radium	Perfect	Fair	Poor	Failure
1	6	M	1	Scalp	14		+	+			
2	4	F	4	Scalp	16		+		+		
				Hand	14		+		+		
				Leg	26		+		+		
				Hip	25	+					+
3	7	M	1	Nose	8		+			+	
4	3	M	1	Nose	8		+		+		
5	24	M	1	Eyelid	17		+		+		
6	13	M	1	Scalp	6		+			+	
7	13	F	2	Knee	18		+			+	
				Scalp	15		+			+	
8	24	M	2	Thigh	10	+					+
				Scalp	7		+			+	
9	14	M	1	Back	35		+			+	
10	8	M	1	Eyelid	8		+			+	
11	24	M	3	Arm	15	+			+		
				Back	18	+			+		
				Scalp	15		+				+
12	12	F	1	Forehead	15	+		+			
13	17	M	1	Lip	18	+		+			
14	10	F	1	Eyelid	8	+		+			
15	14	F	1	Ear	15	+		+			
16	1	M	1	Neck	20	+		+			
17	1	F	1	Scalp	15	+		+			
18	6	F	1	Scalp	6	+		+			
19	17	F	1	Scalp	5	+		+			
20	9	F	1	Neck	5	+		+			
21	12	F	1	Cheek	30	+		+			
22	6	M	1	Neck	25	+		+			
23	36	F	3	Chest	25	+		+			
				Scalp	25	+		+			
				Back	30	+		+			
24	20	F	2	Shoulder	15	+		+			
				Scalp	20	+		+			
25	18	F	2	Scalp	10	+		+			
				Back	30	+		+			
26	24	F	2	Chest	8	+					+
				Scalp	10	+		+			
27	4	F	1	Neck	25	+		+			
28	36	F	1	Neck	5	+		+			
29	29	F	1	Chest	10	+		+			
30	53	F	1	Abdomen	25	+		+			
31	31	F	1	Chest	15	+		+			
32	6	F	1	Back	17	+		+			
33	29	F	1	Back	10	+		+			
34	48	M	1	Chest	10	+		+			
35	49	M	1	Arm	16	+		+			
36	12	M	1	Thigh	20	+		+			
37	9	F	1	Shoulder	15	+		+			
38	13	F	1	Chest	18	+		+			
39	24	F	1	Abdomen	20	+		+			

TABLE 1.—*Clinical Data of Sixty Patients with Hemangiomas*—(Continued)

Case	Age when First Examined, Mo.	Sex	Nevi, No.	Location	Largest Diameter, Mm.	Management		Outcome of Management at Reexamination			
						Conservative	Radium	Perfect	Fair	Poor	Failure
40	13	F	1	Arm	5	+		+			
41	9	F	1	Chest	15	+		+			
42	9	F	1	Elbow	20	+		+			
43	15	F	1	Chest	14	+		+			
44	17	M	1	Abdomen	20	+		+			
45	18	M	1	Perineum	20	+		+			
46	9	F	1	Chest	18	+		+			
47	17	M	1	Glans penis	15	+		+			
48	8	M	1	Perineum	10	+		+			
49	10	F	1	Chest	18	+		+			
50	20	F	1	Abdomen	20	+		+			
51	8	M	1	Back	30	+			+		
52	6	M	1	Chest	5	+		+			
53	8	F	1	Shoulder	20	+		+			
54	24	F	1	Leg	15	+		+			
55	2	F	1	Vulva	5	+		+			
56	3	M	1	Arm	10	+		+			
57	8	F	1	Perineum	18	+		+			
58	3	M	1	Abdomen	8	+		+			
59	1	F	1	Spine	35	+		+			
60	21	F	1	Back	30	+					+

TABLE 2.—*Distribution of Lesions According to Their Size at the Time of Their First Examination*

Largest Diameter, Mm.	Conservatively Treated	Treated with Radium	Total
5	6		6
6-10	12	5	17
11-20	28	7	35
Over 20	12	2	14
Total	58	14	72

outcome of management of each lesion was classified as perfect, fair, poor, or failure.

A result was classified as perfect when the original site of the nevus was completely normal. In other words, no trace of the nevus remained and no scar was left after its disappearance.

A result was considered fair when the nevus disappeared but a scar was left at the site of the nevus, a scar which was level with the surrounding skin and without any retraction of the edges.

A result was considered poor when a disfiguring scar with retraction, depression, and discoloration was the outcome of the treatment.

A result was considered a failure when there had been little or no change in the nevus.

Results

The results of the investigation are summarized in Tables 4, 5, and 6. The relationship of the ultimate fate of each lesion to the mode of treatment is shown in Table 4. As seen in this Table, 87.7% of those treated conservatively had a "perfect" result, while among those treated with radium only 7.14% had a "perfect" result. The two percentages differ by 80.55 (87.70−7.14), which is about 10 times the standard error of their differences, which is 8.02 $\left(\sqrt{\frac{87.7\times12.3}{58}+\frac{7.14\times92.86}{14}}\right)$ The difference, therefore, between the two percentages is statistically very highly significant.

It is also seen in Table 4 that under conservative management only 7.2% of cases resulted in a badly retracted scar or in complete failure. On the other hand, in the radium-treated group 57.14% had similar disappointing results. The difference between these two proportions is 49.94 (57.14−7.2). This is about three and one-half times the standard error of their difference, which is $13.65\left(\sqrt{\frac{7.2\times92.8}{58}+\frac{57.14\times42.86}{14}}\right)$ The difference between these two percentages is therefore also highly significant.

A breakdown of the results in accordance with the location of the lesions on the body surface gave similar results, as is seen

TABLE 3.—*Distribution of Lesions According to Their Location on Body*

Body Sites	Conservatively Treated	Treated with Radium	Total
Spine & back	8	1	9
Face	5	4	9
Scalp & neck	12	6	18
Chest	11		11
Abdomen	5		5
Perineum & sex organs	5		5
Extremities	12	3	15
Total	58	14	72

TABLE 4.—*The Relationship of the Ultimate Fate of the Lesions to the Mode of Management*

Management	Results									
	Perfect		Fair		Poor		Failure		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Conservative	51	87.7	3	5.1			4	7.2	58	100
Radium	1	7.14	5	35.72	7	50	1	7.14	14	100
Total	52		8		7		5		72	

in Table 5. The superiority of the conservative approach over active therapy is most apparent in the more severely affected children, namely, those with vascular nevi on the face. In this group there were four who were treated with radium. Of these, two had badly retracted scars and two had superficial scars. On the other hand, among the five children managed conservatively there were no scars whatever.

The superiority of the conservative approach is similarly obvious in the nevi of the scalp and neck. While all 12 lesions managed conservatively disappeared without any trace, only 1 out of 6 nevi did so among the group treated with radium. Of the remaining five patients, three had a retracted discolored scar and one had a "fair" scar, while a new nevus appeared at the site of the treated one within half a year after the end of the radium irradiation in the fifth patient.

In the more mildly affected patients with nevi over the trunk and the extremities, the method of management appeared to be of little consequence, since in general these nevi would be expected to have disappeared by the age at which the reexamination was

TABLE 5.—*Relationship of Fate of Lesions to the Outcome of Management According to Their Location on the Body*

Body Sites	Management	Results				
		Perfect	Fair	Poor	Failure	Total
Spine & back	Conservative	5	2		1	8
	Radium			1		1
Face	Conservative	5				5
	Radium		2	2		4
Scalp & neck	Conservative	12				12
	Radium	1	1	3	1	6
Abdomen	Conservative	5				5
	Radium					
Perineum & sex organs	Conservative	5				5
	Radium					
Chest	Conservative	10			1	11
	Radium					
Extremities	Conservative	9	1		2	12
	Radium		2	1		3
Total		52	8	7	5	72

TABLE 6.—*Distribution of Lesions According to Their Ultimate Fate in Relation to Their Size*

Largest Diameter, Mm.	Management	Results				
		Perfect	Fair	Poor	Failure	Total
5	Conservative	6				6
	Radium					
6-10	Conservative	10			2	12
	Radium		1	4		5
11-20	Conservative	26	2			28
	Radium	1	3	2	1	7
Over 20	Conservative	9	1		2	12
	Radium		1	1		2
Total		82	8	7	5	72

done. However, the "poor scar" rate of 50% (two out of four nevi) is as high in this treated group as it is in the previous one, whereas no disfiguring scars were observed among the 41 nontreated patients.

In Table 6 are summarized the results of conservative and active management in relation to the size of the nevi. It is apparent from the distribution of the lesions in the perfect, fair, poor, and failure groups that no relationship between the size of the nevi and the indication for active therapy can be postulated.

Comment

The two common categories of hemangiomas differ markedly as regards their prognosis: The flat "portwine" type of lesion nearly always persists, while the raised "strawberry" type of lesion usually disappears spontaneously. Lister,[8] Hopkins,[15] Ronchese,‡ and Wallace[17] have made excellent statistical contributions which prove that, if left untreated for five years or so, many hemangiomas of this kind disappear spontaneously. Other observers have also confirmed this observation.§ According to Wallace, about 10% among 290 strawberry-type nevi have persisted beyond the age of 7 years. Other authors state that more than 90% among the cases observed by them disappear before this age. This is borne out in our series, where failure to regress was found in about 7% of the nevi observed.

However, the problem of whether these lesions have to be treated or not, as well as the problem of determining the most appropriate method of therapy, continues to face the clinician. The former decision presents more difficulties than the latter and provokes more argument. Some clinicians‖ believe that no elevated vascular nevi should be treated in childhood, in the hope that regression will occur later. Others¶ state that all lesions must be treated during infancy, as one cannot predict which nevi will persist and grow.

Such generalizations for or against treatment appear to us fallacious. Rather than that, it seems to us that a more scientific approach to this obviously difficult problem is to try to determine which clinical types require active therapy and which do best by expectant management.

Some attempt has been made to determine the indication for active therapy according to the growth of the nevi in the first months of life. It has been stated that nevi that seem to grow out of proportion

‡ Reference 16, cited by Andrews.[1]

§ References 5, 9, and 11.

‖ References 9 and 11.

¶ References 1, 2, 12, and 20.

to the general growth of the body in this period require active therapy. Wallace,[17] after reviewing the problem, concludes that the disproportionate growth of the nevus usually ceases after the first half year of life and is followed by gradual involution over the next two or three years. The results of our study, presented in this paper, also show that many lesions seen before and after the period of disproportionate growth and followed closely without treatment have disappeared spontaneously. Therefore, it seems apparent that simple disproportionate growth of a nevus during the first few months of life cannot be used as an indication for active therapy of the lesion.

It is apparent from our results that indication for active or conservative management cannot be based on the size of the nevus or its location according to body sites. The only classification that seems to us to meet the requirements of a basis for indication of the kind of treatment for vascular nevi is one based on their functional qualities. According to such a classification, there are three groups of lesions: (*a*) nevi which are cosmetic blemishes, (*b*) nevi which cause functional impairment deformity of a body part, and (*c*) all other nevi.

The advisability of treating a strawberry mark which is a cosmetic blemish is obviously controversial: The physician has to decide whether the final cosmetic result will be improved by active therapy. This will obviously depend on the outcome of the irradiation by x-ray or radium, which are the therapeutic modalities recommended for this age.

A review of the literature seems to indicate that considerable progress has been made during recent years in the radiation therapy of angiomas.# The modern technique of irradiation when done by well-known radiotherapy clinics does not seem to carry a bigger risk of scarring than the *laissez-faire* method of management. This effect, however, is limited to nonulcerated nevi[21] treated early after birth and not later than one year of age.* It appears from the observations of Scholte,[21] Pack and co-workers,[18] and Pendergrass and his associates[20] that hemangiomatous tissue becomes progressively less sensitive to radiation therapy with age; a better result may be expected at an earlier age with a smaller dose of radiation. According to the observations of Scholte[21] and Pfahler,[18] if the nevus is ulcerated as a result of trauma or any other cause, a more visible scar as an aftermath of irradiation is inevitable.

The fact that spontaneous disappearance occurs and is unaccompanied by anything more than the faintest of scarring usually does not, in our opinion, justify the risk of leaving the patient with a significant cosmetic defect, whether in the form of a disfiguring scar as a result of delay of active therapy or as a prominent red mass if the nevus fails to regress spontaneously, as predicted. When the lesion is in a conspicuous area we consider it necessary to try to hasten involution by irradiation. In very few patients so treated will the ultimate results be inferior to the results of spontaneous involution.

The nevi which cause functional impairment deformity usually present clinically hemorrhage and ulceration. When ulceration occurs, it usually involves the whole surface and because of the poverty of the blood flow through the nevi the process of repair is rather slow.

In these cases, the question of therapy depends on the position and the size of the hemangioma and the general health of the child. However, in the majority of these nevi early radiation treatment is to be advised and carried out in order to prevent ulceration and severer functional impairment deformity later in life.

Nevi which do not or may not cause a functional impairment deformity or are not a cosmetic blemish fare best when left to their natural course. The conservative management of these lesions will result in al-

References 1, 18, 20, 21, and 22.

* References 20 and 18.

most all cases in spontaneous disappearance of the nevus, with no scarring whatever. Therefore, one is not justified in introducing the hazards and expense of treatment. The parents of children with this kind of nevus should be cautioned against active therapy. They can be reassured by the fact that these nevi are rarely seen in the adult, not because all of these lesions are treated in infancy but simply because they almost always disappear spontaneously. However, if by the age of 7 years the lesion has not disappeared plastic surgical therapy could be advised. Our previous experience with carbon dioxide snow has convinced us that this form of therapy of even small lesions is undesirable, because of the deep ulcerations observed in its course, which are a natural localization of purulent processes, and the disfiguring scars left after it.

Summary

A follow-up examination of 60 children with the strawberry type of vascular nevus of the skin showed that, whenever the lesion was left to follow its natural course, it resolved without any residual scarring. Fifty-four among fifty-eight nevi had so disappeared. It is concluded that the majority of vascular nevi fare best when left to their natural course. With the exception of nevi which are cosmetic blemishes or such that cause functional impairment deformity, no active therapy is to be undertaken. The problem of the treatment of the latter two types of lesions is discussed.

REFERENCES

1. Andrews, G. C.; Domonkos, A. N., and Post, C. F.: Treatment of Angiomas: Summary of 20 Years Experience at Columbia Presbyterian Medical Center, Am. J. Roentgenol. 67:267, 1952.

2. Strandqvist, M.: Radium Treatment of Cutaneous Cavernous Hemangiomas, Using Surface Application of Radium Tubes in Glass Capsules, Acta radiol. 20:185, 1939.

3. Falk, W.: Indications for Surgical Treatment in Childhood, Dapim Refuiim 7:255, 1948.

4. Nelson, W. E.: Textbook of Pediatrics, Ed. 6, Philadelphia, W. B. Saunders Company, 1954, p. 1465.

5. Walter, J.: Birthmarks and Moles, Lancet 1:475, 1951.

6. Holmdahl, K.: Cutaneous Hemangiomas in Premature and Mature Infants, Acta Paediat. 44:370, 1955.

7. Bowers, R. E.: Treatment of Haemangiomatous Naevi with Thorium X, Brit. M. J. 1:121, 1951.

8. Lister, W. A.: Natural History of Strawberry Naevi, Lancet 1:1429, 1938.

9. Bivings, L.: Spontaneous Regression of Angiomas in Children: 22 Years Observation covering 236 Cases, J. Pediat. 45:643, 1954.

10. Annotations, Birthmarks and Moles, Lancet 1:158, 1951.

11. Anderson, C. R.: Treatment of Vascular Nevi, J. Pediat. 25:148, 1944.

12. Modlin, J. J.: Capillary Hemangiomas of the Skin, Surgery 38:169, 1955; abstracted, J. A. M. A. 159:520, 1955.

13. Pack, G. T., and Miller, T. R.: Hemangiomas: Classification, Diagnosis, and treatment, Angiology 1:405, 1950.

14. Matthews, D. N.: Treatment of Haemangiomata, Brit. J. Plastic Surg. 6:83, 1953.

15. Hopkins, J. G.: Vascular Nevus with Spontaneous Involution, Arch. Dermat. & Syph. 43:1033, 1941.

16. Ronchese, F.: Hemangiomas: Should Treatment be Expectant or Active? Rhode Island M. J. 29:658, 1946.

17. Wallace, H. J.: The Conservative Treatment of Haemangiomatous Nevi, Brit. J. Plast. Surg. 6:78, 1953.

18. Pfahler, G. E.: The Treatment of Birth Marks, Fortschr. Geb. Röntgenstrahlen 75:141, 1951; Abstracted Am. J. Roentgenol. 68:850, 1952.

19. Brown, J. B.; Fryer, M. P., and McDowell, F.: Hemangiomas, Ann. Surg. 137:652, 1953.

20. Pendergrass, E. P.; Katterjohn, J. C., and Butchart, J. B.: Some Considerations in Treatment of Hemangioma in Infants and Young Children, Am. J. Roentgenol. 60:182, 1948.

21. Scholte, P. J. L.: Aperçu du traitement des angiomes dans la clinique radiothérapeutique de l'Hôpital universitaire de Leyde de janvier 1946, jusqu'en mai 1949 (308 cas), Acta radiol. 36:241, 1951.

22. Katterjohn, J. C.: The treatment of hemangioma, J. Indiana M. A. 41:903, 1948; abstracted, Excerpta Med. XIV 3:305, 1949.

Studies on Carbohydrates in the Body Fluids

I. Identification by Means of Paper Chromatography

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Standard biochemical methods for the determination of simple sugars in biological fluids depend on the chemical reduction of alkaline copper solutions by the sugar present. They give no indication of the qualitative differences between reducing sugars, nor do they indicate the presence of a nonreducing sugar, such as sucrose, nor that the reducing substance is a sugar. The frequent occurrence of reducing sbstances in the urine and the need to identify nondextrose sugars in the blood have prompted the use of paper chromatography as a means of qualitatively identifying the sugars present in the body fluids.[1] The commonly used methods of fermentation and biochemical color reactions lack the specificity of chromatography. This presentation will describe the methods and their application in the identification of simple sugars in the blood, urine, and breast milk.

Kowkabany[2] and Isherwood[3] have described the many techniques, solvent systems, and spray reagents useful in the identification of the numerous classes of carbohydrates by paper chromatography. The identification of reducing substances in the urine has been reported,* as well as studies on monosaccharides in pentosuria,[6] neuromuscular disorders,[7] galactosemia,[8] and Gaucher's disease.[9]

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From the Department of Pediatrics, University of California School of Medicine. John and Mary Markle Scholar in the Medical Sciences (Dr. Ulstrom).

* References 4 and 5.

Materials

Apparatus

1. Pipettes, calibrated to contain 0.1 ml.
2. Glass centrifuge tubes, 12 or 15 ml.
3. Micropipettes, sizes calibrated to deliver from 2.5 microliters to 250 microliters.
4. Folin or Folin-Wu sugar tubes graduated at 6.25 ml.
5. Lyophilization apparatus.
6. Whatman No. 1 filter paper; 22×7 in. sheets.
7. Chromatography assembly. Glass cylinders 12 in. in diameter and 24 in. high; equipped with glass cover, solvent trays, and metal racks.
8. Two shallow 12×24 in. enamel finish photographic developing trays.

Reagents

1. Blood sugar reagents.[10]
2. Ethanol, 100%.
3. Standard sugar solution. A 1% solution containing lactose, galactose, dextrose, fructose, and xylose prepared using reagent grade sugars and distilled water.
4. Solvent: Upper phase of a 2:5:7 mixture of pyridine, ethyl acetate, and water (Reagent grades).
5. Silver nitrate (Reagent grade), saturated solution in H_2O.
6. Silver nitrate-acetone solution, prepared by adding 0.1 ml. saturated $AgNO_3$ solution to 30 ml. acetone (C. P.). Add water dropwise with shaking until the precipitate dissolves. Prepare solution immediately before use.
7. Approximately 0.2 N NaOH (Reagent grade).
8. Photographic acid fixer.† Prepare according to directions on label.
9. Lloyd Reagent (hydrated aluminum silicate).

Methods

I. *Preparation of Blood for Chromatography.*—A. Protein-Free Filtrate: One-tenth milliliter of capillary blood is washed into a centrifuge tube containing 1.5 ml. of distilled water; 0.2 ml. of barium hydroxide is added, the tube agitated, and

† Kodak Acid Fixer.

after the solution has turned brown, 0.2 ml. zinc sulfate is added. The solution again is mixed thoroughly and then centrifuged. The supernatant fluid is collected and filtered through a Pyrex wool plug using air pressure. (Pyrex wool is preferred over glass because of its flexibility and ease in handling.)

B. Total Reducing Substance: The determination of total reducing substance is carried out according to methods described by Nelson,[10] with one modification. Two hundred fifty microliters each of the protein-free filtrate, copper reagent, and arsenomolybdate color reagent are used instead of the usual 1 ml. This modification requires the use of sugar tubes graduated at 6.25 ml.

C. Chromatography: One milliliter of the remaining protein-free filtrate is then lyophilized. Approximately 0.1 ml. absolute alcohol is added to redissolve the sugars. Substances which may interfere with the chromatogram are not freely soluble in the alcohol, and its volatile nature aids in keeping the chromatogram spot small. The solution should be applied to the chromatogram as soon as possible to prevent evaporation of the alcohol.

II. *Preparation of Urine for Chromatography.*—Urine is prepared according to methods suggested by Fales.[11] To 5 ml. of urine, add 1 gm. of Lloyd reagent and 5 ml. 1/20 N oxalic acid. The mixture is agitated for 15-20 minutes, filtered, and the clear filtrate is applied directly to the chromatogram. The method removes salts and organic substances which may interfere with the proper development of the chromatogram. Alternate methods which give equally satisfactory results are those suggested by Tower and co-workers,[7] using anionic-cationic exchange resins, or by precipitating interfering substances with two parts each $Ba(OH)_2$ and $ZnSO_4$ and one part urine.[8]

III. *Preparation of Breast Milk for Chromatography.*—Three to five milliliters of breast milk is centrifuged to allow excess fat to accumulate at the surface where it forms a thick coagulum and can be removed or the lower layer decanted. The remaining lipids are then extracted three times with petroleum ether and by centrifugation. One part of the fat-free portion is precipitated with two parts $Ba(OH)_2$ and two parts $ZnSO_4$. The mixture is filtered and the filtrate is applied to the chromatogram.

IV. *Preparation of Papers.*—Seven by twenty-two-inch strips of Whatman No. 1 chromatography paper are flow washed in a standard chromatogram cabinet with three complete washings of 0.1 N HCl. The papers are then washed with distilled water until the reaction of the wash flowing from the ends of the papers is neutral to litmus. Serration of the ends of the papers with pinking shears facilitates an even flow of the solutions off the paper. The papers are then dried and stored for future use.

The chromatograms are spotted at 1-in. intervals along a line 3 in. from the end of the paper. The spots are kept as small as possible (½ in. or less) with the aid of a stream of warm air from a hair dryer. If necessary, it is possible to apply 100 or more microliters in multiple applications to a small area. The quantity of "total-reducing substance" determined as outlined above, will serve as a guide in determining the amount of material to be applied to the paper. In general, 25 micrograms equivalent of total reducing substance is the upper limit that should be placed on the paper; amounts greater than this cause trailing, distortion, poor resolution, and inadequate separation on the chromatogram. Five microliters of a (1%) solution of lactose, galactose, dextrose, fructose, and xylose is applied at the extreme left- and right-hand positions on the paper to serve as reference standards.

V. *Solvent System.*—The solvent system found most suitable is the upper phase of a pyridine, ethyl acetate, and water mixture in a ratio of 2:5:7.‡ Since pyridine has a strong and disagreeable odor, preparation of the solvent should be carried out in a fume hood.

VI. *Development of the Chromatogram.*—Four chromatograms may be developed in a descending direction in cylinders 24 in. high and 12 in. in diameter, employing the solvent system described above. It is advisable to develop four papers at the same time, since this aids in maintaining a highly saturated atmosphere within the cylinder and speeds the development time. The cylinders need not be equilibrated prior to introduction of the solvent nor is it necessary to maintain a constant temperature during development. The entire procedure is conducted in a fume hood.

The chromatograms are allowed to develop for at least 14 hours and during this period the solvent will run off the serrated end of the paper strip. This is necessary in order to allow separation of galactose and dextrose, since their migration rates (RF values) are similar. At the end of the development the solvent is siphoned from the trays and the chromatograms allowed to dry while still in the cylinders.

VII. *Identification of Reducing Substances on Chromatogram.*—When dry, the chromatogram is dipped in a silver nitrate acetone solution so as to completely and evenly wet the paper. It is then air dried and immersed in a tray of 0.2 N NaOH solution. In a few seconds the sugars will begin to appear as dark-brown spots against a light-brown background. The color development should be allowed to proceed for at least two minutes, as some of the sugars develop their colors slowly.

‡ References 12 and 13.

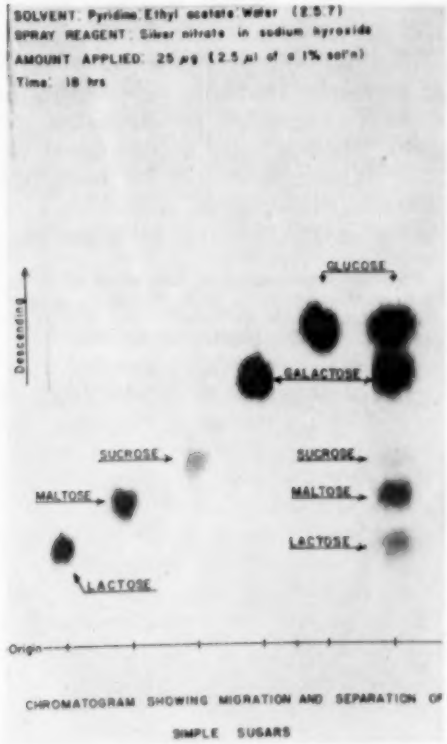


Fig. 1.—Chromatogram of standard sugar solutions.

There is no danger in over-developing the chromatogram.

When the color development has proceeded to completion, usually in about three minutes, the chromatogram is transferred to a tray containing an acid fixer of the type commonly used in processing photographic papers. The wet chromatogram is very easily torn, but can be handled conveniently with one end folded over a short glass rod.

In the fixing bath the brown background color disappears, leaving the sugars as brown spots against a white background. The method is very sensitive and less than 1 microgram of sugar can be detected. The process requires close attention, since the fixing time varies depending on the amount of sodium hydroxide being carried into the fixing solution, as well as variations in the thickness of the filter paper. Over-fixation will cause excessive clearance of the paper and render small quantities of sugars nondetectable. The papers clear slightly in a washing process, and it is best to remove the papers to the wash while some background color is still apparent. In general, more information is to be gained from a chromatogram that is slightly discolored than from one which has been excessively cleared. Some experience is necessary to gain maximum contrast between the sugar spot and the background color.

Slight agitation of the acid fixer will speed the fixing time and insure an even reaction over the entire sheet of paper. When the time for fixation becomes prolonged, the fixer should be discarded and a new solution used.

After fixing, the papers are allowed to wash in running water for at least one hour. After the chromatograms have been washed and dried, the sugars appear as black or gray spots against a white background. The chromatograms can then be inspected for reducing substances. They may be stored for long periods of time without fading.

Results

I. *Standard Solutions.*—Results obtained in separation and identification of standard sugar solutions are shown in Figures 1 and

Fig. 2.—Chromatogram of standard sugar solutions.

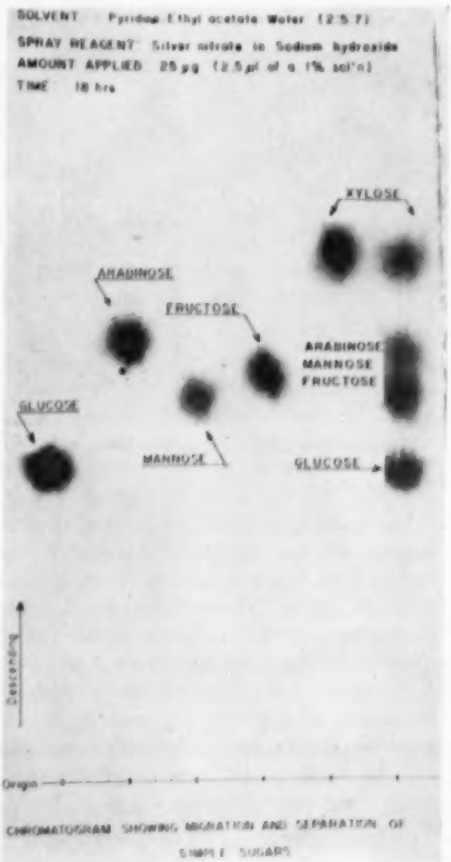
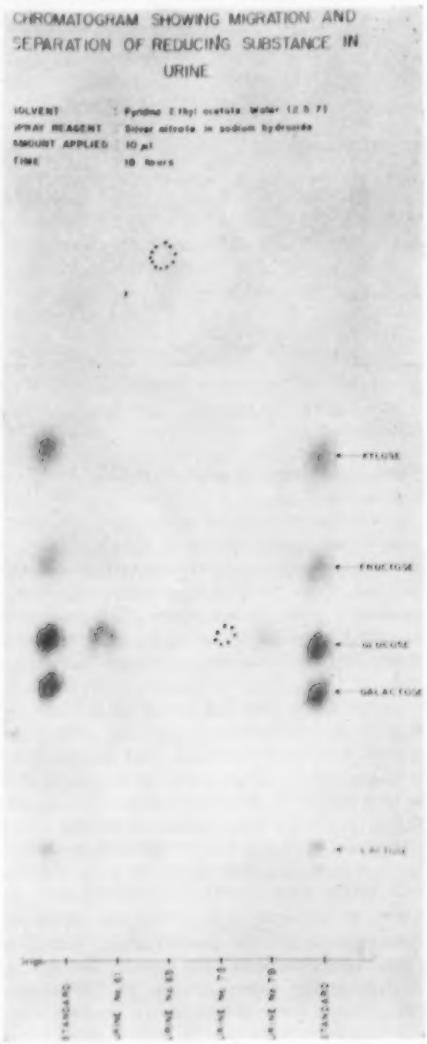


Fig. 3.—Chromatogram of four urine specimens negative with Benedict's reagent. Note absence of reducing sugars.

2. In Figure 1 there is clear separation of all sugars. Sucrose shows some variability in its reaction, since it has no free keto or aldehyde group to react with the $AgNO_3$. Partial hydrolysis may occur in the NaOH solution during color development and permit identification. Figure 2 shows the poor separation usually obtained with arabinose, fructose, and mannose. Identification must then be made by differential spraying with aniline and phloroglucinol sprays.§ Xylose and ribose (not shown) show good separation and are easily identified.

II. *Urine.*—Figure 3 is a chromatogram of four urine specimens, each negative to Benedict's reagent and prepared as outlined under "Methods." Ten microliters was applied to each position. As noted, the chromatogram shows no evidence of a reducing reaction associated with the pres-

Fig. 4.—Chromatogram of four urine specimens, each showing reaction with Benedict's reagent. Sugars present are as follows: No. 61, 70, 79, dextrose; No. 79, xylulose (xyloketose).



§ References 4 and 14.

ence of carbohydrates except for the reference standards. A faint "half-moon" spot can be seen near the origin of urine No. 74: This is frequently present in normal urines and is presumed to be glucuronic acid.‖ A "bleaching effect" is routinely seen in the area corresponding to the position of fructose, but does not interfere with the identification of sugars in this area.

Figure 4 shows chromatograms of urine specimens, each of which had a "trace" or "positive" reaction with Benedict's reagent. Dextrose (glucose) was present in urines No. 61 and 79. In urine No. 65 a definite spot, indicated by the dotted circle, was found which had migrated well in advance of xylose. Subsequent color development of another similar chromatogram with aniline and phloroglucinol sprays identified the sugar as most likely xylulose (xyloketose).¶ Urine No. 70 contained a faint trace of dextrose which does not appear on the photograph and is indicated by the dotted circle.

The methods described here will usually demonstrate reducing substance only when the Benedict's reaction is also positive, i. e., a trace or more. Depending on the concentration of reducing substance as determined by the strength of the Benedict's reaction, it has been found that 5 to 25 microliters of the prepared urine is sufficient to identify a reducing substance on the chromatogram. Larger amounts of urine will, of course, bring out sugars that are normally present in the urine. Tower and co-workers [7] applied 150 microliters of urine and identified xylose, arabinose, dextrose, and ribose in normal urines. Other sugars including lactose, galactose, fructose, arabinose, and xylose have been identified in urines by the techniques described .

III. *Breast Milk.*—Figure 5 is a chromatogram of three samples of human breast milk during the first few days of lactation. Lactose is demonstrated in large quantities. Dextrose (glucose) is demonstrated in small quantities in samples 211 and 214.

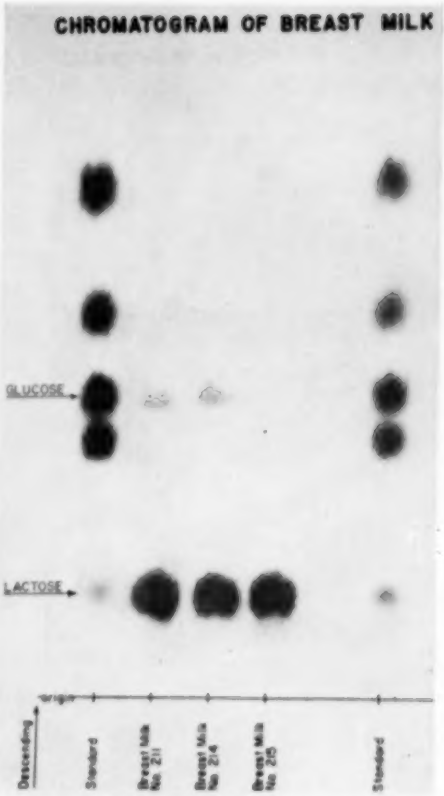


Fig. 5.—Chromatogram of breast milk showing large amounts of lactose in all specimens and dextrose in No. 211 and 214.

IV. *Blood.*—Chromatograms of the blood following administration of galactose to a normal 9000-gm. infant are shown in Figure 6. Galactose is definitely demonstrated in the 60 minute specimen, although a trace may be present at 30 minutes. The total blood sugar at the same intervals is noted across the bottom of the chromatogram. Chromatograms of the urine revealed galactose as late as three hours after administration.

V. *Galactosemia.*—Figure 7 shows blood from two infants with galactosemia.# The first infant, No. 199, was a 16-month-old

‖ References 4 and 6.

¶ References 4 and 6.

All specimens on these patients were provided by George Donnell, M.D., Los Angeles Children's Hospital, Los Angeles.

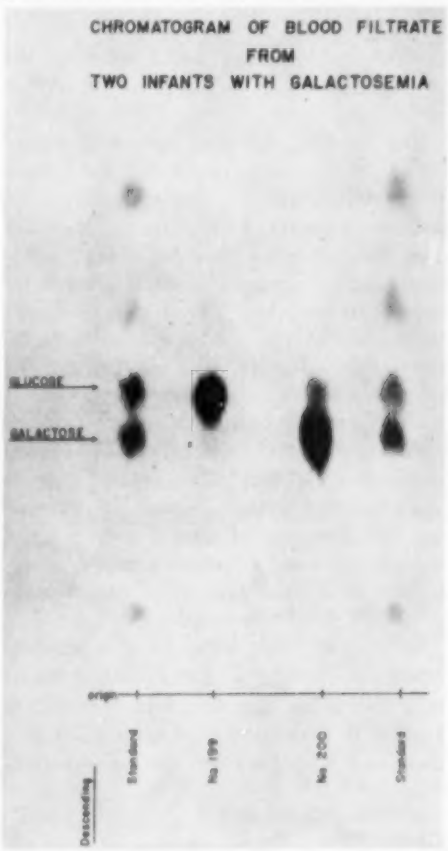
Fig. 6.—Chromatogram of blood filtrates following administration of 16 gm. galactose to 9000-gm. infant.

infant with cataracts, hepatomegaly, and mental retardation. A reducing substance in the urine was identified as galactose. At the time the specimen of blood was taken, the infant had been on suboptimal fluid intake and was virtually fasting; consequently no galactose could be identified in the blood. The second infant, No. 200, was a one-month-old infant who died one hour after admission with probable sepsis. Hepatomegaly and cataracts were present, and the urine contained galactose. The blood filtrate shown in the chromatogram contains a large quantity of galactose and a small amount of dextrose.

Figure 8 shows a galactose tolerance test done on the 16-month-old infant with galactosemia (No. 199). The fasting specimen revealed no galactose, as the infant was on a lactose-free diet. However, with the ingestion of galactose, there is a tremendous increase in the blood galactose, in amounts exceeding the dextrose and persisting throughout the five hours. The reducing substance migrating just ahead of the dextrose was not identified.

V. *Fructose Tolerance Tests.*—Figure 9 demonstrates the results of infusion of 100 cc. of a 10% fructose solution over a 15-minute period to a 4-month-old infant. Fructose is present in the blood for a two-hour period following the infusion, and was found in the chromatograms of the urine

Fig. 7.—Chromatogram of blood filtrates from two infants with galactosemia. No. 199 shows no galactose because of dietary control.



for 95 minutes following infusion (not shown).

Comment

The techniques described here should permit further study of the qualitative utilization of carbohydrates in infants and children. Previous studies, hampered by nonspecific chemical procedures and need for large volumes of blood, may be simplified by chromatographic procedures employing micro quantities of blood and providing accurate identification of substances. In addition to these general problems, certain specific areas for future investigation may be mentioned.

The importance of dextrose in the maintenance of a normally functioning central nervous system is well recognized. The fetus, as well as the newborn, may derive

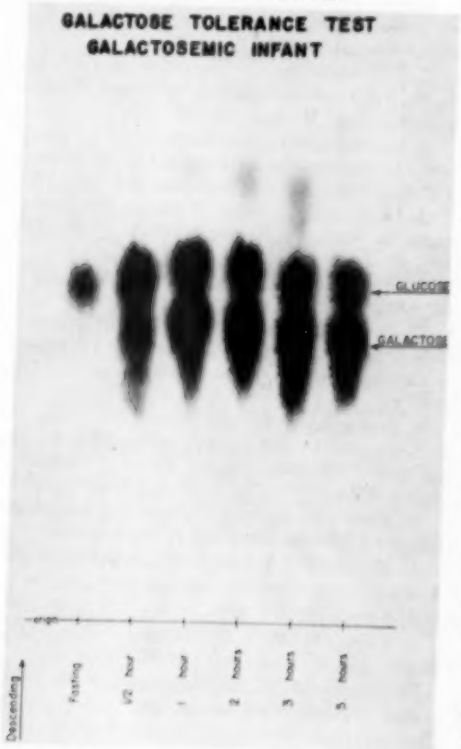


Fig. 8.—Chromatogram of blood filtrates from galactosemic infant (No. 199, Fig. 7) following ingestion of galactose (1.75 gm/kg.).

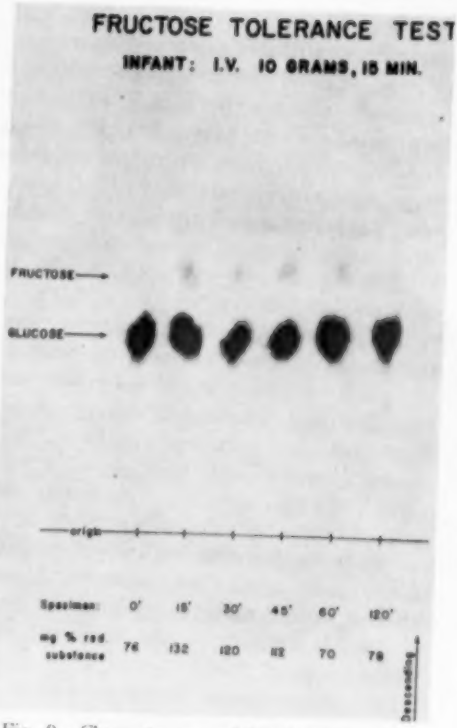


Fig. 9.—Chromatogram of blood filtrates from infant receiving 100 cc. 10% fructose (Levugen) solution (10 gm. fructose) I. V. in 15-minute period.

his carbohydrate from sources other than dextrose and by enzymatic action convert them to dextrose. Whether partial failure of this conversion can occur is not known, although Hartman's data suggest that in prematures and normal infants the galactose derived from the breakdown of lactose in milk may be inadequately converted to dextrose.[15] Hartman has also described a similar inadequate conversion of galactose to dextrose in sick infants following milk feedings.[15] Galactose was identified by fermentation methods. The chromatographic methods described here should be valuable in confirming these findings, since they will permit an accurate identification of galactose in the blood.

The presence of other nondextrose reducing substances in the blood deserves additional study. Fructose has been re-

ported in the fetal blood of animal species [16] and man.[17] Utilizing chromatographic techniques, we have also tentatively identified a reducing substance in cord blood which migrates at the same rate as fructose. Blood fructose concentrations are high in the sheep fetus during the early months of gestation [18]; whether this is true for the human fetus is not known. The methods described here, using 0.1 cc. of blood, would be applicable to this type of study.

The presence of nonsugar reducing substances in the blood has recently been investigated by Cochrane and associates, who have described a method to distinguish between the total reducing substance ("apparent sugar"), and total sugar ("true sugar").[19] This difference represents the nonsugar reducing substances ("N. S. R.") present in the blood and in normal subjects is equivalent to 13.4 mg. dextrose. Using different chromatographic techniques it may be possible to identify this nonsugar reducing fraction.

The chromatogram shown in Figure 5 agrees with the accepted observation that lactose is the principal sugar present in breast milk. When measured by standard chemical techniques, the large amounts of lactose may obscure the finding of small amounts of nonlactose sugars. These may be easily identified, as for example the dextrose (glucose) in Figure 5, by chromatographic techniques. The ability of the mammary glands to secrete other nonlactose sugars is a subject for study by these methods.

The value of chromatographic procedures for the identification of sugars in the urine has been described previously.* It is particularly useful in identifying trace amounts of sugars in urines that show reduction with Benedict's reagent. Positive identification of dextrose in the urine of new diabetics, or the coexistence of other reducing sugars in the urine may be established with these techniques.

* References 1, 4, 5, 6, 7, 8, and 11.

Summary

Chromatographic techniques for the qualitative study of simple carbohydrates in the blood, urine, and breast milk have been presented. The application of these techniques to the investigation of carbohydrate utilization in the infant and child has been noted. Specific areas of interest include the investigation of galactose utilization in the normal and sick infant, the presence of fructose in the fetus, and the possible identification of nonsugar reducing substances in the blood. These techniques are also useful in identification of reducing sugars in the urine and in breast milk.

REFERENCES

1. Ulstrom, R. A., and Wright, S. W.: Paper Chromatography of Sugar and Its Use in Pediatrics, in Essays on Pediatrics in Honor of Dr. Irvine McQuarrie, edited by R. A. Good and E. S. Platou, Minneapolis, Lancet Publications, Inc., 1955.

2. Kowkabany, G. N.: Paper Chromatography of Carbohydrates and Related Compounds, Advances in Carbohydrate Chem. 9:303, 1954.

3. Isherwood, F. A.: Separation of Carbohydrates and Phosphoric Esters on Paper Chromatograms, Brit. M. Bull. 10:202, 1954.

4. Horrocks, R. H., and Manning, G. B.: Partition Chromatography on Paper: Identification of Reducing Substances in Urine, Lancet 1:1042, 1949.

5. Eastham, M.: Paper Partition Chromatography of Sugars in Urine, Biochem. J. 45: xiii, 1949.

6. Flynn, F. V.: Essential Pentosuria, Brit. M. J. 1:391, 1955.

7. Tower, D. B.; Peters, E. L., and Pogorelskin, M. A.: Nature and Significance of Pentosuria in Neuromuscular Disease, Neurology 6:37; 125, 1956.

8. Lockhart, J. D., and Roboz, E.: Case of Galactosemia Identified in a 4-Day-Old Infant by Paper Chromatographic Technic, Pediatrics 13:211, 1954.

9. Woolf, L. I.: Sugar-Containing Lipids of Gaucher's Disease, Biochem. J. 56: xvi, 1954.

10. Nelson, N.: A Photometric Adaption of the Somogyi Method for Determination of Glucose, J. Biol. Chem. 153:375, 1944.

11. Fales, F. W.: Identification of Urinary Sugar, Am. J. Clin. Path. 25:336, 1955.

12. Jermyn, M. A., and Isherwood, F. A.: Improved Separation of Sugars on Paper Partition Chromatogram, Biochem. J. 44:402, 1949.

13. Koch, R. B.; Geddes, W. F., and Smith, F.: The Carbohydrates of Gramineae: I. The Sugars of the Flour of Wheat (Triticum Vulgare), Cereal Chem. 28:424, 1951.

14. Partridge, S. M.: Aniline Hydrogen Phthalate as a Spraying Reagent for Chromatography of Sugars, Nature, London 164:443, 1949.

15. Hartmann, A. F.: Pathologic Physiology in Some Disturbances of Carbohydrate Metabolism, J. Pediat. 47:537, 1955.

16. Goodwin, R. F. W.: Foetal Fructose in Various Mammals, Nature, London 170:750, 1952.

17. Hagerman, D. D., and Villee, C. A.: The Transport of Fructose by the Human Placenta, J. Clin. Invest. 31:911, 1952.

18. Bacon, J. S. D., and Bell, D. J.: Fructose and Glucose in the Blood of the Foetal Sheep, Biochem. J. 42:397, 1948.

19. Cochrane, W. A.; Payne, W. W.; Simpkiss, M. J., and Woolf, L. I.: Familial Hypoglycemia Precipitated by Amino Acids, J. Clin. Invest. 35: 411, 1956.

Idiopathic Pulmonary Hemosiderosis

Report of a Case with Apparent Remission from Cortisone

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Idiopathic pulmonary hemosiderosis is a rare disease of children and young adults with a well-defined clinical course of hypochromic anemia, intermittent pulmonary bleeding, progressive pulmonary fibrosis, and eventual terminal cardiorespiratory failure. The disease may run a less malignant course in the older child and young adult with prolonged remissions and perhaps eventual recovery. The cause of the malady has yet to be defined other than by speculation based on observation of the clinical course and pathological findings at autopsy.

The disease was first recognized by Ceelen [1] in 1931, when he described the autopsy examination of two children with pulmonary fibrosis and massive hemosiderin deposition limited to the Lung. Wyllie [2] presented the most comprehensive description of the disease in 1948 and added seven cases to the literature. There have been about 40 cases described in English literature, and 9 cases have been recognized and reported in this country.* Our patient has had a remission of over one year apparently induced by cortisone. Owing to the fact that the disease is so rare and the physiopathologic mechanism involved is obscure, the following case is described in detail.

Report of a Case

The patient is a 16-year-old white boy who became ill in April, 1953, with the gradual onset of fatigue, pallor, lack of energy, and shortness of breath when climbing stairs. He was first examined in June, 1953, at which time he appeared pale, thin, and chronically ill. He weighed 86 lb., oral temperature was 100.6 F, pulse was 88 beats per minute and regular, a few crepitant rales were heard at the lung bases, and there was a soft, Grade 2 systolic murmur at the apex. The red blood cell count was 3,180,000 per cubic millimeter; hemoglobin, 5.9 gm. per 100 ml.; white blood cells, 8750 per cubic millimeter; sedimentation rate, 25 mm. (uncorrected) Westergren in one hour. Chest x-ray was essentially normal.

Treatment consisted of rest and oral ferrous sulphate. He gradually gained weight, and the anemia improved. In August, 1953, he weighed 93 lb. and the hemoglobin was 12.4 gm. per 100 ml. He returned to school and remained in relatively good health except for a mild hypochromic anemia that persisted despite continued iron medication. In July, 1954, he weighed 111 lb., the red blood cell count was 4,700,000 per cubic millimeter, and the hemoglobin was 11.4 gm. per 100 ml.

First Hospital Admission.—He was again seen Oct. 25, 1954, at which time he was hospitalized for a period of 16 days. He complained of fatigue, lack of energy for two weeks, and had fainted twice in the previous 12 hours. He had discontinued the iron medication two months previously. The positive findings on physical examination were pallor, a soft Grade-2 apical systolic murmur, pulse 100 and regular, oral temperature of 100 F. The spleen was enlarged and extended 3 cm. below the left costal border and the liver was palpable at the right costal border, but neither was tender. The lungs were clear to auscultation and percussion.

Chest x-ray showed a diffuse finely mottled density throughout the entire lung fields. This was most marked in the central portion of the lungs. There was moderate enlargement of the hilar nodes (Fig. 1).

The red blood cell count was 3,240,000 per cubic millimeter; hemoglobin, 4.7 gm. per 100 ml.; white blood cell count, 11,250 per cubic millimeter, with 62% neutrophiles, 25% lymphocytes, 11% stab cells, 2% monocytes, 1% eosinophiles. The peripheral blood smear showed poikilocytosis, anisocytosis, and an occasional nucleated red cell. The spinal fluid was normal. Sternal bone marrow showed erythroid hyperplasia. Sternal marrow and blood cultures were negative for fungi and pathogenic organisms; cephalin flocculation, negative in 24 hours and 2+ in 48 hours; total serum protein, 5.95 gm. per 100 ml.; with A/G ratio of 3.7/1;

* References 3-9.

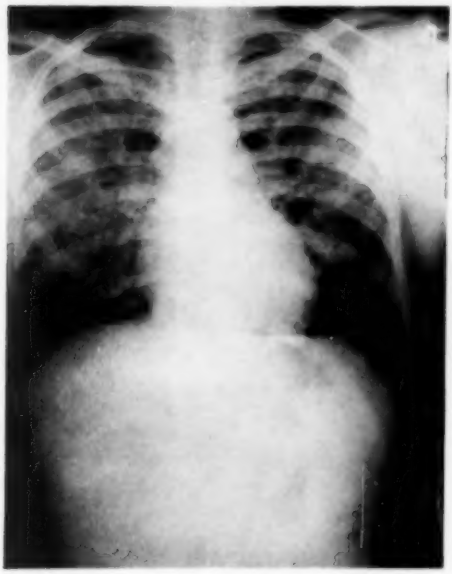

Fig. 1.—X-ray of the chest, Oct. 23, 1954, shows a very fine mottled density throughout the entire lung fields except for the extreme right apex and each costophrenic angle. This density appears to be due to small dense infiltrates varying from less than 1 up to 3 mm. in size, giving the appearance of a diffuse pneumonitis. There are large hilar glands bilaterally which measure 2×2 cm. in size and are discrete. The heart shadow is normal. There are a few 3- or 4- mm.-diameter areas of calcification in the right hilum and in the periphery of the right lung.

serum bilirubin, 0.95 direct and 1.40 total; urinalysis, normal and negative for porphyrin; bleeding time, 1 minute 42 seconds; coagulation time, 4 minutes, and 42 seconds; and blood type O was Rh negative. The following tests were negative: tuberculin test, stool for occult blood and ova, polyagglutination, heterophile antibody, cold agglutinins. The electrocardiogram was normal.

He had a temperature of 101 to 102 F rectally for the first two days and a normal temperature the remaining days in the hospital. Treatment consisted of oral ferrous sulfate, and transfusion of 1 liter of blood. The final blood count was 3,620,000 red blood cells per cubic millimeter; hemoglobin, 10.5 gm. per 100 ml.; hematocrit, 38 vol. %. There was almost complete clearing of the infiltration on the chest x-ray except for a small residual extending outward from both hila. He was discharged asymptomatic Nov. 9, 1954.

Interim.—He remained at rest at home, but in the evening of Nov. 26, 1954, he experienced a tight sensation in the chest with shortness of breath and coughed up one or two teaspoonsful of bright red blood. When he was seen the following morning, the physical findings were normal except for tachycardia of 110 and an oral temperature of 100 F. The red blood cell count was 4,040,000 per cubic millimeter, and the hemoglobin was 12.7 gm. per 100 ml. A chest x-ray showed a diffuse finely granular density in the right midlung field extending outward from the hilum (Fig. 2).

Second Hospital Admission.—He was admitted to the hospital for further studies Dec. 4, 1954. He complained of tightness of the chest and had coughed up about one teaspoonful of bright red blood the night before. He had maintained an intermittent low-grade fever of 100 F to 101 F since his previous hospitalization. Physical findings were as before.

Further tests were obtained as follows: Histoplasmin skin test, negative; stool, positive for occult blood; nonprotein nitrogen, 41.0 mg. per 100 ml.; thymol turbidity 0.4 units; cephalin flocculation, negative in 24 and 48 hours; 3,860,000 red blood cells per cubic millimeter and 11.7 gm. hemoglobin per 100 ml.; red cell fragility normal with hemolysis beginning at 0.42% sodium chloride solution and complete at 0.36% solution; platelets, 280,000 per cubic millimeter (indirect method); direct Coombs test, negative. The serum iron was 161 micrograms per 100 ml. which is within the normal range. Chest x-ray on December

Fig. 2.—X-ray of the chest, Nov. 26, 1954, shows a diffuse clouding extending downward from the right hilum and apparently involving the right middle lobe. There is more of the finely granular mottling extending all the way up to the level of the right clavicle with very little change in the left chest.

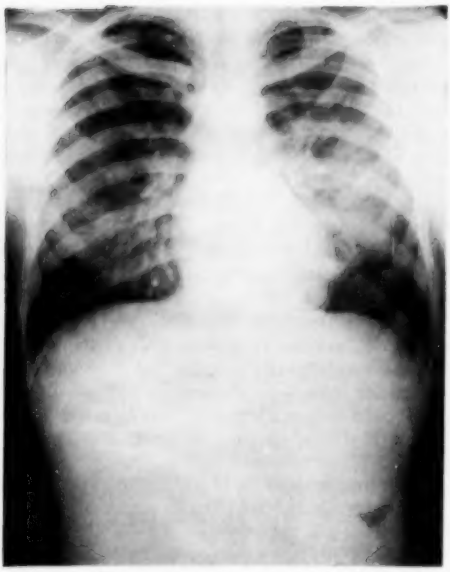

Fig. 3.—X-ray taken Dec. 6, 1954, shows that the density in the right chest is much less now than on Nov. 26, 1954. There is a large area of increased density involving the middle two-thirds of the left chest, which was not present on the previous examination. This has the same finely granular density that was present on the previous x-rays.

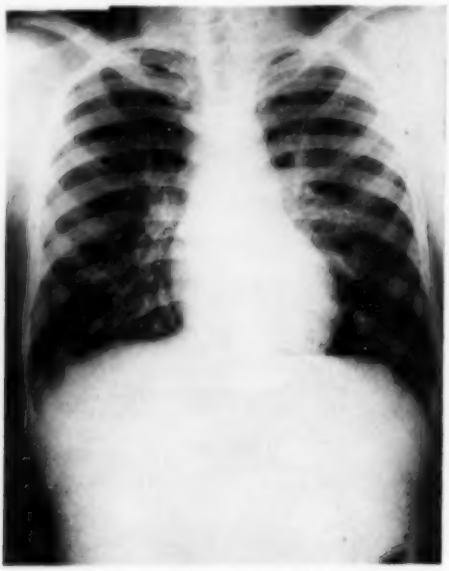

Fig. 4.—X-ray taken Dec. 11, 1954, shows marked clearing of the increased density in the left chest and further regression of the mottling in the right lower chest. There is a minimal finely nodular infiltration persisting in the middle two-thirds of the left lung. The hilar adenopathy is less pronounced.

6 showed a marked decrease in the density on the right side but there was an extensive finely granular density in the left midlung field (Fig. 3). X-ray of the chest four days later showed marked clearing of the density in the left lung and further regression of the infiltration in the right lung as noted in the film of Nov. 26, 1954, and there was partial regression of the hilar adenopathy (Fig. 4).

Treatment consisted of bed rest and oral ferrous sulphate. He was discharged asymptomatic Dec. 13, 1954.

Present Status.—Since discharge from the hospital he had repeated episodes of tightness of the chest, hemoptysis, low-grade fever, and fatigue. Hemosiderin-laden macrophages were present in great numbers in sputum and fasting gastric aspiration obtained Dec. 18, 1954 (Fig. 5). Jan. 7, 1955, he coughed up several teaspoonsful of bright red blood. Fluoroscopic examination of the chest showed massive infiltration in the left lung. Oral cortisone was started that day at 200 mg. the first two days, 100 mg. the next seven days, and then 75 mg. daily in divided doses. Mild episodes decreasing in severity, consisting of cough, hemoptysis, mild fever, and dyspnea, occurred every few weeks thereafter for nearly eight months. April 12, 1955, he weighed 132 lb. and felt better than he had for more than two years; vital capacity, 3.9 liters (93% of normal); blood count, normal; and the chest x-ray showed no pulmonary fibrosis.

Oct. 10, 1955, he experienced the last episode of pulmonary bleeding and he has now remained symptom-free for nine months. Cortisone was gradually reduced in dose and discontinued Oct. 30, 1955. At present the vital capacity is 4.2 liters, or 97% of normal, and the x-ray of the chest is clear except for a diffuse finely granular infiltration which is most pronounced in the central areas of the lungs.

Family History.—The family history was essentially negative except that the mother, who is 34 years old and of mixed European descent, had a history indicating a bleeding tendency. As a child she had frequent and severe epistaxis that required hospitalization on two occasions. She hemorrhaged from the tonsillar area one week following tonsillectomy at the age of 5 years. She developed menorrhagia at the age of 29 with menstrual periods lasting two weeks. Hysterectomy was done two years later because of the excessive menstrual flow with secondary anemia. The pathological diagnosis was "myometrial and endometrial hypertrophy."

Comment

Idiopathic pulmonary hemosiderosis most commonly occurs in children from several

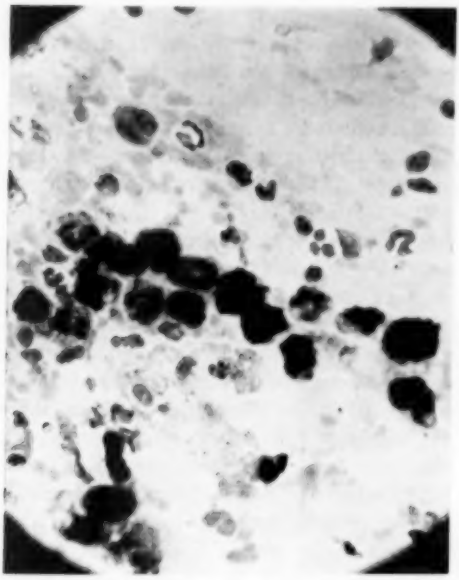

Fig. 5.—Photomicrograph of sputum expectorated by patient, Dec. 18, 1954. The macrophages in the sputum are laden with deep blue staining granules of hemosiderin. The cells with hemosiderin were readily seen in repeated sputum and gastric aspiration specimens. (Prussian blue reaction, × 600.)

months to 16 years of age, but several cases have been observed in young adults. There is no hereditary or familial predisposition and the sexes are equally susceptible. The course is intermittent, progressive, and usually fatal within several weeks to several years. The few cases that have survived have been older children or young adults.

The clinical course is characteristic and will suggest the diagnosis if the observer is aware of the syndrome. The onset is usually insidious. The child is pale, tires easily, has intermittent fever, and shortness of breath. The initial symptoms and the presence of the soft precordial systolic murmur of anemia may lead one to suspect rheumatic fever. On further observation one will observe that the child experiences acute episodes of tightness in the chest, shortness of breath, rapid heart beat, and mild hacking cough. With progression of the illness fleeting cyanosis, hemoptysis, abdominal pain, and vomiting may accompany the acute episodes. The acute symptoms may last several hours to several days and gradually subside. The patient is subsequently symptom-free for weeks or months except for pallor and fatigue. During the acute episode, the physical findings in the chest are usually minimal despite the rather alarming symptoms. Scattered crepitant rales or slight consolidation may be detected by careful examination. Tachycardia of 110 to 140 beats per minute is the rule. If the bleeding is severe there may be transient right heart failure with hepatosplenomegaly, precordial gallop rhythm, and sudden cardiac enlargement. Following the acute symptoms transcient icterus may be detected. As the disease progresses, the dyspnea and tachycardia persist, pallor and asthenia increase, and hemoptysis and at times hematemesis is the rule. The signs of pulmonary fibrosis and cor pulmonale appear with cyanosis, orthopnea, clubbing of the digits, and progressive enlargement of the spleen and liver. The child may die suddenly early in the course of the disease with massive pulmonary hemorrhage, but usually lives on to die later of right heart failure, pulmonary fibrosis, and pneumonia. An occasional case has not followed the usual fatal course, but has experienced spontaneous remissions of increasing duration, indicating that complete recovery may occur.

The infiltration seen in the chest roentgenogram taken during the acute episode is rather striking in contrast to the minimal physical findings in the chest. The infiltration is characteristically finely granular or mottled and may be extensive. It is frequently centrally located but may be found in the periphery of the lung. It is usually irregular in distribution and tends to migrate. It appears abruptly with the symptoms of acute respiratory distress and changes rapidly in character and distribution from day to day and usually disappears within a week or two. With repeated acute episodes, the diffuse finely nodular, as well as the reticular infiltration of pulmonary

fibrosis appears throughout the lungs and persists. The hilar lymph nodes are moderately enlarged and dense. The pulmonary conus may be prominent and the right side of the heart enlarged.

The peripheral blood picture is that of hypochromic anemia of chronic blood loss. The bone marrow is normal or shows erythroid hyperplasia. The commoner blood dyscrasias are ruled out by normal values for the following tests: bleeding and coagulation time, platelet count, prothrombin time, tourniquet test, and red cell fragility. There may be transient elevation of the serum bilirubin and occult blood in the stool following the acute episode. The most significant laboratory test is the finding of hemosiderin-laden macrophages in the sputum or in the fasting morning gastric aspiration. The hemosiderin appears as clumps of yellow-brown granules in the cytoplasm of the macrophages. The granules stain a deep blue with the Prussian blue reaction of potassium ferrocyanide and hydrochloric acid. If the cells cannot be obtained in the sputum or gastric fluid, aspiration needle biopsy of the lung has proved valuable without undue risk to the patient.

The confirmation of the clinical diagnosis is established at postmortem examination. The lungs are firm and reddish brown in color. The gross appearance is that of diffuse fibrosis. The tracheobronchial and bronchopulmonary lymph nodes are enlarged, firm, and reddish brown. The right ventricle of the heart is usually dilated and the wall hypertrophied.

Evidence of chronic bleeding into the lung is manifested by diffuse deposition of hemosiderin in the lung, visceral pleura, and hilar lymph nodes.

The pigment is contained within the macrophages or reticuloendothelial cells in the air spaces, connective tissue spaces, lymph nodes, and epithelial cells of the alveoli. It is the hemosiderin that imparts the reddish brown hue to the tissues involved. More recent bleeding is indicated by the presence of red cells in the alveoli, bronchioles, and interstitial spaces. There is an extensive proliferation of connective tissue throughout the lung. In addition to the focal hemorrhages, the hemosiderin deposition, and the extensive proliferation of reticulum, the most characteristic and perhaps most significant finding is degeneration of the elastica. The elastic strands of the lung framework and even of the arteries, arterioles and veins, are fragmented, deficient, or completely absent.

Pulmonary hemosiderosis secondary to mitral stenosis with chronic pulmonary hypertension and hemochromatosis are to be considered in the differential diagnosis. The former is characterized by a history of rheumatic fever and typical clinical findings of mitral stenosis. The latter is recognized by bronze skin pigmentation, cirrhosis, and diabetes.

The etiology of the illness remains an enigma. The loss of blood into the lung is thought to be a process of diapedesis of red cells through altered vascular walls. McLetchie [10] postulated a defective vasomotor control of the pulmonary vessels with massive capillary dilatation and extensive diapedesis of red cells into the lung tissues. Wyllie [2] and Ceelen [1] suggested that there is a congenital deficiency of elastica in the lungs resulting in relatively rigid lungs and defective pulmonary ventilation and with impaired pulmonary function there follows capillary blood stasis and tissue hypoxia resulting in increased permeability of the capillary vessels and massive diapedesis of red cells into the lung tissue. However, Steiner [11] pointed out that the autopsy findings in three children previously reported with fulminating disease of several months' duration failed to show deficiency or destruction of elastic tissue. This evidence indicates that the destruction of elastic tissue is secondary to and not the cause of pulmonary bleeding. He noted three cases previously reported that improved after splenectomy. He reported the fourth case, of a 6-year-old boy who experienced a decrease in the severity and frequency of the

pulmonary bleeding following splenectomy. He theorized that the permeability of the lung capillaries is altered by an antigen-antibody reaction in an "autosensitized" person and thus introduced the concept of autoimmunization. The definitive role of the spleen in this autosensitization state is not understood, but it is considered part of the reticuloendothelial system responsible for antibody formation. The nature of the antigen is not defined, nor is the mechanism of the altered permeability of the pulmonary capillaries explained in his report.

The usual treatment is inadequate and is limited to relief of symptoms. In the early stage oral ferrous sulfate and blood transfusions are beneficial, as well as rest and avoidance of emotional and physical strain. With acute pulmonary hemorrhage, rest in bed is imperative. In the late stage of chronic cardiorespiratory incapacity, digitalis, oxygen, and antibiotics offer support.

The role of splenectomy in the treatment has not been established. The episodes of bleeding are apparently less severe and less frequent after removal of the spleen, but further follow-up study is needed before this procedure can be accepted as a cure.

Our patient is the second reported that has received adrenal cortical steroid therapy. Browning and Houghton reported a case in a 29-year-old man who experienced a remission after receiving corticotropin (ACTH) and then maintained on cortisone.[9] We appreciate the fact that definite conclusions cannot be drawn from two cases but believe that adrenal cortical steroid therapy should be considered early in the treatment of this disease.

Summary and Conclusions

The case report of a 16-year-old boy with idiopathic pulmonary hemosiderosis treated with cortisone is presented in detail. The apparent decrease in the severity of the bleeding following adrenal cortical steroids tends to lend evidence in favor of the theory of autoimmunization, as proposed by Steiner. The role of the spleen has not been determined. Since a few cases [12] have shown spontaneous remission and apparent recovery without specific treatment, it is not possible to determine the therapeutic value of adrenal cortical steroids or splenectomy from the results obtained in a few cases. However, we believe that early treatment with corticotropin (ACTH) or adrenal cortical steroids is justified and that splenectomy should be considered in those cases that progress despite adrenal cortical steroids. Early diagnosis and aggressive management are desirable so that permanent pulmonary tissue injury may be averted.

REFERENCES

1. Ceelen, W.: Die Kreislaufstörungen der Lungen, in Handbuch der speziellen pathologischen Anatomie und Histologie, edited by F. Henke and O. Lubarsch, Vol. 3, Berlin, J. Springer, 1931, pp. 1-163.

2. Wyllie, W. G.; Sheldon, W.; Bodian, M., and Barlow, A.: Idiopathic Pulmonary Hæmosiderosis, Quart. J. Med. 17:25 (Jan.) 1948.

3. Anspach, W. E.: Pulmonary Hemosiderosis, Am. J. Roentgenol. 41:592 (April) 1939.

4. Pilcher, J. D., and Eitzen, O.: Pulmonary Hemosiderosis in a 6 Year Old Boy: A Clinical and Pathological Report, Am. J. Dis. Child. 67:387 (May) 1944.

5. Luther, G.: Idiopathic Pulmonary Hemosiderosis, Cincinnati J. Med. 30:546, 1949.

6. Gellis, S. S.; Reinhold, J. D. L., and Green, S.: Use of Aspiration Lung Puncture in the Diagnosis of Idiopathic Pulmonary Hemosiderosis, A. M. A. Am. J. Dis. Child. 85:303 (March) 1953.

7. Schaar, F. E., and Rigler, L. G.: Idiopathic Pulmonary Hemosiderosis, Essential Brown Induration of the Lungs, Essays on Pediatrics in Honor of Irving McQuarrie, Minneapolis, Lancet Publications, Inc., 1955, p. 232.

8. Wigod, M.: Idiopathic Pulmonary Hemosiderosis: Report of a Case in Early Childhood with Severe Anemia, New England J. Med. 253:413 (Sept. 8) 1955.

9. Browning, J. R., and Houghton, J. D.: Idiopathic Pulmonary Hemosiderosis, Am. J. Med. 20: 374 (March) 1956.

10. McLetchie, N. G. B., and Colpitts, G.: Essential Brown Induration of the Lungs (Idiopathic Pulmonary Haemosiderosis), Canad. M. A. J. 61:129 (Aug.) 1949.

11. Steiner, B.: Essential Pulmonary Haemosiderosis as an Immuno-Haematological Problem, Arch. Dis. Childhood 29:391 (Oct.) 1954.

12. Hamer, N. A. J.: Idiopathic Pulmonary Haemosiderosis in a Young Adult, Brit. M. J. 4920:1008 (April 23) 1955.

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Recognition and Treatment of the Various Seizure Disorders in Medical Practice. Lewis Levy and Edward Shanbrom.—p. 599.

Treatment of Chronic Granulocytic Leukemia with Myleran.—The authors studied 24 patients with chronic granulocytic leukemia ranging in age from 2 to 72 years. These patients were treated with Myleran for periods ranging from 1 to 13 months. The leucocyte counts were reduced to normal levels initially in all the patients and the level of immature cells found in the peripheral blood was also reduced. Correction of anemia is a prominent feature of Myleran therapy, and there is also improvement in subjective symptoms. Myleran appears to be a valuable addition to the anti-leukemic armamentarium, but the effect of this drug on life expectancy of the patient with chronic granulocytic leukemia is not known.

Idiopathic Paroxysmal Myoglobinuria. Report of Two Cases and Evaluation of the Syndrome.—Idiopathic paroxysmal myoglobinuria is a rare disorder and is a sign of muscle necrosis due to a variety of causes. In the idiopathic variety, which occurs in paroxysms, the myoglobinuric episode is characteristically, but not invariably, related to muscular effort. The authors review the 21 cases in the literature and add 2 more cases of their own. The disease had its onset during childhood in about one-third of the cases. The common symptoms are muscle pain and weakness and a paralysis typically involving the lower extremities but often involving other muscle groups as well. Urine discoloration by myoglobin is observed for one or more days after an attack. Four of the patients reported died—one of respiratory failure due to necrosis of respiratory muscles and three of acute tubular necrosis of the kidneys. There is no pathologic evidence that the disease has any relation to the muscular dystrophies. The etiology of the muscle necrosis which gives rise to the myoglobinuria is at present unknown.

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Combined Lesions of Basal Ganglia, Medulla Oblongata, and Spinal Cord in a Ten Year Old Boy. Erna Christensen, J. Melchior, and P. Plum.—p. 396.
Inorganic Pyrophosphate in Human Blood? Carl-Eric Raiha, G. Aberg and G. R. Wallgren.—p. 415.
High Protein Nutrition in Prematures by Means of Casein Supplement to Human Milk. Arne Rothe-Meyer and Erik Sandoe.—p. 419.
Pseudo-Hirschsprung bei einem Myxodem-Saugling. Toivo Salmi and Pirkko Lahesmaa.—p. 428.
Kartagener's Triad: Situs Inversus, Bronchiectasis, and Sinusitis: Report of a Case. Tage Samsoe-Jensen.—p. 433.
Spinal Cord Tumors in Children. Sture Siwe.—p. 437.
The Significance of Electro-Encephalographic Spike Foci in Patients With Cerebral Palsy Without Epileptic Seizures. Marit Skatvedt and Arne Lundervold.—p. 440.
Baby Pig Mortality and Infantile Pyloric Stenosis. O. Steinicke Neilsen.—p. 444.
Atypical Pneumonia in an Infant, Associated with APC Virus Infection. Goran Sterner.—p. 449.
The Falling Rate of Breast-Feeding in Sweden. Justus Strom.—p. 456.
Anaemia Hypoplastica Congenita Treated with Cortisone: Correction of the Anaemia with Cortisone Treatment During Four Years. Alfred Sundal.—p. 456.
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The Geographical Distribution of Iron-Deficiency Anaemia in Childhood. Bo Vahlquist.—p. 468.
Chemotherapy in Primary Tuberculosis. Arvid Wallgren.—p. 472.
Congenital Dysplasia of the Hip Joint in the Newborn Babies. Theodor Walther.—p. 476.
Recurrent (Allergic?) Swelling of the Parotid Gland. Knud Wilken-Jensen.—p. 480.
Chronic Cerebral Fever in Cerebral Palsy: Temperature Athetosis. Lea Ylppo and Arvo Ylppo.—p. 484.

Methemalbuminemia in the Neonatal Period with Special Reference to Hemolytic Disease of the Newborn.—Methemalbumin concentrations in the serum of 10 normal newborns and 14 full-term Rh isoimmunized infants were studied. This heme pigment was found to be present in low concentration in 3 of 10 normal infants and was noted to disappear from the blood during the first day of life.

In erythroblastosis the methemalbumin level was found to be extremely high in most cases with findings to suggest an intense hemolytic process in utero, and was usually associated with an elevation in serum hemoglobin level. The methemalbumin concentrations did not, however, vary consistently, and in some cases requiring exchange transfusion this pigment could not be detected.

The significance of methemalbumin in hemolytic disease of the newborn is briefly discussed and its accumulation thought to be due to intense hemolysis in addition to hepatic dysfunction. It was concluded that the concentration of methemalbumin in serum cannot be used as a guide to exchange transfusion therapy.

Prolonged Icterus Neonatorum and Myxoedema.—Of 11 infants with congenital myxedema, 5 were noted to have had jaundice starting at age 2-3 days and persisting for at least 3 months. The icterus had, in all cases, the appearance of a prolonged

physiologic icterus and other causes of jaundice were felt to be excluded. It was postulated that this persistence of jaundice is due to a prolonged immaturity of hepatic and renal function associated with a thyroid state.

Strikingly high birth weights were found in four of these five infants with jaundice and in four of the six nonicteric infants with congenital myxedema; it was suggested that high birth weight may be a characteristic of this disturbance.

The fact that prolonged physiologic icterus may be the first sign of myxedema and, therefore, help in arriving at an early diagnosis was emphasized.

American Heart Journal, St. Louis

52, No. 1 (July) 1956

* The Significance of the Pulmonary Vascular Bed in Congenital Heart Disease: I. Normal Lungs; II. Malformations of the Heart in Which There is Pulmonic Stenosis. J. Francis Dammann Jr. and Charlotte Ferencz.—p. 7.

The Mechanism of Cough Syncope. Henry D. McIntosh, E. Harvey Estes, and James V. Warren.—p. 70.

The Relations of Pectus Excavatum to Heart Disease. Fred W. Wachtel, Mark M. Ravitch, and Arthur Grishman.—p. 121.

Fibroelastosis in Adults. Samira R. Guraieb and R. H. Rigdon.—p. 138.

The Management of Cor Pulmonale in Chronic Pulmonary Disease, with Particular Reference to the Associated Disturbance in the Pulmonary Circulation. Alfred P. Fishman and Dickson W. Richards.—p. 149.

52, No. 2 (Aug.) 1956

* The Significance of the Pulmonary Vascular Bed in Congenital Heart Disease: III. Defects Between the Ventricles or Great Vessels in Which Both Increased Pressure and Blood Flow May Act upon the Lungs and in Which There Is a Common Ejectile Force. J. Francis Dammann Jr. and Charlotte Ferencz.—p. 210.

Transposition of the Aorta and Levoposition of the Pulmonary Artery. A de Caralho Azevedo, A. Ney Toledo, A. Alves de Carvalho, and Robison Roubach.—p. 249.

The Significance of the Pulmonary Vascular Bed in Congenital Heart Disease: I. Normal Lungs; II. Malformations of the Heart in Which There Is Pulmonic Stenosis.—The importance of the pulmonary vascular bed in the evolution of the clinical course of congenital heart disease is gaining increasing recognition. The authors present the first part of a study of the anatomic alterations of the pulmonary vascular bed as they occur in normal persons and in patients with a variety of cardiac defects resulting in abnormal pulmonary hemodynamics.

The study is based on lung sections obtained by biopsy or postmortem examination from patients with normal cardiorespiratory systems and from patients with congenital heart disease. The small muscular pulmonary arteries were studied and a lumen: wall ratio obtained by dividing the diameter of the lumen by twice the thickness of the media and intima together. The thickness of the individual layers of the vessels was recorded, and qualitative changes in the vessels and in the lung parenchyma were also assessed. The results were correlated with the age of the patients.

The present paper deals with the evolution of the pulmonary vascular bed in the normal person with clear-cut anatomic pulmonic stenosis.

At birth, in the normal subject, the small intrapulmonary artery structurally resembles the small artery and arteriole of the systemic circulation with a small lumen, thin intima and thick media and adventitia. Thus, the lumen:wall ratio is low. Within four weeks later, progressive changes started to take place consisting in a relative and absolute increase in the lumen size and a thining of the media so that, except for the presence of an elastica interna and externa, the pulmonary vessels took on the appearance of small veins. Although there is considerable variation in the rate of evolution of the pulmonary vascular changes, almost all normal infants have passed a lumen:wall ratio of 2.5 by 6 to 10 months of age. These anatomic changes would seem to bear a close relationship to the progressive fall in pulmonary vascular resistance occurring from infancy to adulthood.

Patients with pulmonic stenosis revealed an essentially normal pattern of evolution of the pulmonary vascular bed. This is to be expected in as much as pulmonary artery pressure is low and pulmonary blood flow is low to normal. The changes noted in the vascular bed in cases of pulmonic stenosis included the presence of bronchial collateral circulation and thrombosis in the pulmonary arteries both of which are related to polycythemia and anoxia.

The Significance of the Pulmonary Vascular Bed in Congenital Heart Disease: III. Defects Between the Ventricles or Great Vessels in Which both Increased Pressure and Blood Flow May Act upon the Lungs and in Which There is a Common Ejectible Force.—This article is the second in a series dealing with pulmonary vascular changes in congenital heart disease. The previous article dealt with the evolution of the pulmonary vascular bed in the normal person and in the person with pulmonic stenosis. The current article correlates the clinical course with the microscopic findings in the lungs of patients in whom the pulmonary vascular bed is exposed to high blood flows at systemic pressures. The malformations studied which resulted in such abnormal pulmonary hemodynamics included ventricular septal defect, single ventricle, patent ductus arteriosus, and aortic septal defect.

The authors have divided the anatomic changes in the pulmonary vascular bed in the above types of defects, with their associated clinical manifestations, into three phases. As in the first article, the pulmonary vasculature is evaluated on the basis of the lumen:wall ratio of the small pulmonary arteries and on the presence or absence of medial hypertrophy, adventitial thickening, and intimal proliferation.

In Phase I, following birth, the usual thinning of the small fetal pulmonary arteries occurs. Microscopically these vessels will have thin medias and adventitias without intimal thickening. The result is a high lumen:wall ratio. In association with this, pulmonary resistance falls and pulmonary blood flow increases at the expense of systemic blood flow. A compensatory increase in cardiac output follows, eventually leading to high output cardiac failure.

If the patient survives Phase I, changes occur in the pulmonary vascular bed in the form of thickening of the media with reduced lumen:wall ratios. The result is an increase in pulmonary vascular resistance approaching systemic resistance. A state of circulatory balance then exists in which the patient may be symptom free, cyanosis is minimal or absent, and no significant cardiac enlargement occurs. This state is classified by the authors as Phase II. Clearly, not all patients in whom the pulmonary vascular bed is exposed to systemic pressures at high flows pass through Phase I to arrive at Phase II. In some there is retention of the thick-walled, small-lumen fetal arteries present at birth, and this patient passes into Phase II without going through the sequence of changes leading to Phase I.

The final stage, classified as Phase III, represents a progression from Phase II in which, as a response to increased pressure and flow, in addition to medial hypertrophy, there is intimal proliferation in the small pulmonary arteries leading to almost complete obliteration of some of the vessels. Under these circumstances pulmonary resistance exceeds systemic resistance, the shunt becomes right to left, and cyanosis is manifest.

The importance of these pulmonary vascular changes as they influence the decision for surgery is obvious. Patients in Phase I and II are candidates for corrective surgery when possible. Once Phase III has been reached, it is probable that surgery can no longer be successfully carried out, inasmuch as a significant decrease in intimal proliferation in the pulmonary arteries is unlikely to occur, and, if the defect permitting the right to left shunt is closed, the right ventricle will be obliged to function at a pressure exceeding systemic pressure. Under these circumstances irreversible right ventricular failure ensues. A question still to be answered is when in the course of the disease do the pulmonary vascular changes become so severe that surgery is contraindicated.

American Journal of Medical Sciences, Philadelphia

231, No. 1 (Jan.) 1956

The Skin Response to a Nicotinic Acid Ester: An Acute Phase Reaction. W. Weiss.—p. 13.
* The Effects of Thyrotropin and Desiccated Thyroid upon Hypothyroidism with Goiter. R. P. Levy, L. W. Kelly Jr., and W. McK. Jefferies.—p. 61.
The Sprue Syndrome. J. C. S. Paterson.—p. 92.

231, No. 2 (Feb.) 1953

* Myocarditis in Viral (Epidemic) Hepatitis. O. Saphir, G. D. Amromin, and H. Yokoo.—p. 168.

Observations on the Source of Elevated Plasma Ammonia Levels in Hepatic Insufficiency. H. J. Zimmerman and R. J. Korn.—p. 177.
The Ocular Manifestations of Hypercalcemia. H. P. Wagener.—p. 218.

231, No. 3 (March) 1956

* Complications of Meningococcus Infection in a Series of Sixty-Three Consecutive Sporadic Cases. J. L. Tobin.—p. 241.
Epidemiological Aspects of Cases of Blastomycosis Admitted to Memphis, Tenn., Hospitals During the Period 1922-1954: A Review of Eighty-Six Cases. E. W. Chick, W. D. Sutliff, J. H. Rakich, and M. L. Furcolow.—p. 253.
Recent Advances in the Laboratory Diagnosis of Tuberculosis. R. W. Reed and O. Morgante.—p. 320.

231, No. 4 (April) 1956

* Clues to Better Understanding of the Nature and Treatment of Certain Infectious Diseases. T. E. Woodward.—p. 369.
The Problem of Subclinical Rheumatic Carditis. C. G. Tedeshi and B. M. Wagner.—p. 382.
Hemorrhagic Diathesis with Increased Capillary Fragility Caused by Salicylate Therapy. P. G. Frick.—p. 402.

231, No. 5 (May) 1956

Glossopharyngeal Breathing as an Aid to Recovery from Paralytic Poliomyelitis. W. D. Loeser.—p. 487.
Recent Contributions to Diuretic Therapy. W. Modell.—p. 564.

231, No. 6 (June) 1956

* The Recovery of Poliomyelitis Viruses from Fecal Samples of Poliomyelitis Patients and Household Contacts. C. A. Miller and P. Kamitsuka.—p. 607.
Observations on Certain Viruses Causing Exanthematous Diseases in Man. J. F. Enders.—p. 622.
The Effect of Corticotrophin (ACTH) on Ammonia Production in the Nephrotic Syndrome. G. H. Heidorn. —p. 644.
The Heart in Progressive Muscular Dystrophy. F. Grandell.—p. 659.
Pediatrics—The Turnover and Circulation of the Plasma Proteins in the Body. R. J. Slater and A. Sass-Kortsak.—p. 669.

232, No. 1 (July) 1956

The Treated Pulmonary Lesion and Its Tubercle Bacillus: I. Pathology and Pathogenesis. W. E. Loring and H. MacVandiviere.—p. 20.
The Treated Pulmonary Lesion and Its Tubercle Bacillus: II. The Death and Resurection. H. MacVandiviere, W. E. Loring, I. Melvin, and S. Willis.—p. 30.
An Evaluation of the Single Breath Technique for Measuring Anatomic Respiratory Dead Space with the Nitrogen Meter. R. H. Wilson, B. E. Jay, P. L. Richburg, and R. Evans.—p. 67.

232, No. 2 (Aug.) 1956

A Comparison of the Metabolism of Rubidium 86 and Potassium 42 Following Simultaneous Injection into Man. M. P. Tyor and James S. Eldridge.—p. 186.
Surgery—Current Concepts Concerning the Surgical Treatment of Pulmonary Tuberculosis. R. T. Crowley. —p. 198.
Ophthalmology—Lesions of the Optic Nerve: An Exophthalmus of Endocrine Origin. H. P. Wagener.—p. 226.

The Effects of Thyrotropin and Dessicated Thyroid upon Hypothyroidism with Goiter.—Seven patients, six children and one adult, with clinical hypothyroidism and goiter were the subjects of this study. None of the patients were from the same family; there was no history of ingestion of goitrogens or of iodine deficiency. Histologic examination of the glands was not done. All seven received a single test injection of thyrotropin (TSH), 5 units intramuscularly; three hours thyroid uptake of I^{131} was compared before and after (24 hrs) the injection, PBI (protein-bound iodine) in the blood was similarly measured before and after. Four patients who were not receiving treatment had elevated thyroid I^{131} uptake before the injection, and no further response followed administration of the TSH. In these four patients, two had PBI levels in the range considered hypothyroid by the authors; one was definitely elevated and the other was normal. The latter alone showed a rise in PBI following TSH injection. Three patients had been on replacement treatment at the time of this study. They had elevated thyroid I^{131} uptakes and low blood PBI levels before TSH injection. TSH administration failed to significantly alter the PBI level or I^{131} thyroid uptakes. The authors observed striking improvement in the hypothyroid symptoms following replacement with dessicated thyroid accompanied by lowering of the thyroid I^{131} uptake and return of the PBI to normal. Under this treatment the goiter diminished in size. They infer from their study that this syndrome they describe is caused by defective thyroid hormone synthesis in the gland's cells.

Myocarditis in Viral (Epidemic) Hepatitis.—Four cases of clinically diagnosed acute viral hepatitis are described briefly. Three were adults and one was a 6-year-old boy. In all instances careful study of cardiac tissue revealed acute myocarditis and examination of the liver and other tissues was characteristic of acute hepatitis. The cardiac lesions were typically minute foci of necrosis and a diffuse serous inflammation. In three of the four the bundle of His was involved showing necrosis of isolated fibers, hemorrhage, and inflammatory exudate. Two of the patients had electrocardiographic abnormalities probably caused by the myocarditis. The authors comment concisely on the incidence of myocarditis in other viral diseases, pointing out that it has been demonstrated in poliomyelitis, measles, mumps, viral pneumonia, and encephalitides.

Complications of Meningococcus Infection in a Series of Sixty-Three Consecutive Sporadic Cases.—Over a four-year period at an Air Force recruit training base, 63 cases of meningococcic meningitis appeared among a constantly shifting population of approximately 15,000 young adults. Most of the cases were seen in March and April, although cases occurred in all months. Therapy consisted of penicillin and sulfadiazine; contacts were all treated with sulfadiazine. Of the 63 cases, 32 (50.8%) were complicated and 6 (9.8%) died. The complications can be listed as follows: Waterhouse-Friderichsen syndrome 9 (14.3%), nerve involvement 17 (27%), Pulmonary edema 1 (1.6%), nephritis and pneumonia 1 (1.6%), gastrointestinal hemorrhage 2 (3.2%), erythema nodosum 1 (1.6%), skin ulceration 7 (11.2%), Stevens-Johnson syndrome 1 (1.6%), and electrocardiographic changes 6 (9.5%). Since some cases had more than one complication, the percentages given indicate the number of times the particular complication was seen among the total 63 cases. The author draws attention to the high incidence in this series because the patients were diagnosed and treated early in the disease. He further stresses that out of the six deaths, four were from the Waterhouse-Friderichsen syndrome. In the management of the latter he was not impressed with the use of intramuscular cortisone and felt that norepinephrine was of more immediate aid. Nerve involvement included eye-muscle paresis, hearing loss, herpes zoster, sensory loss, and facial paralysis. Ten cases are abstracted.

Clues to Better Understanding of the Nature and Treatment of Certain Infectious Diseases.—The author considers the problem of the metabolic effects on the host which pathogenic organisms induce. The newly awakened interest in the fundamental nature of infections by which pathogenic agents irreversibly damage living cells and alter tissues is reviewed briefly using specific examples. These include the following headings: Role of capillaries and small blood vessels in pathogenesis of disease; Persistence of micro-organisms in the host and the relapse problem; Nature of underlying lesion, and the problem of Plague as related to time of therapy and toxemia.

He envisions in the future that treatment of serious infections will entail two stages, (1) administration of an antibiotic for microbial control and (2) the administration of an essential metabolic substance or substrate necessary for proper cell function. The paper is particularly important for those dealing with the pediatric age group wherein infection occurs more frequently.

The Recovery of Poliomyelitis Viruses from Fecal Samples of Poliomyelitis Patients and Household Contacts.—This study was conducted during the 1954 field trials of the poliomyelitis vaccine in Kansas, Missouri, and Oklahoma. Virus isolations were made in tissue culture and the virus typed using the same technique. First-, second-, and third-grade children residing in these areas who developed clinical poliomyelitis and their household contacts were accepted for study. Stool specimens were obtained as soon as possible from the patient and contacts after poliomyelitis was diagnosed. In this area only second-grade children had been vaccinated.

There were 35 households with a total of 192 persons. In each of these homes one person had been clinically diagnosed as poliomyelitis. There were an additional 21 persons in these households diagnosed as having an illness or symptom compatible with poliomyelitis or "minor illness." Among the household contacts, symptoms were commonest in children 4 to 5 years old.

Virus isolations were attempted on stools from 227 persons within six weeks of the first symptoms in a family member. The figure (227) includes additional case

studies not a part of the 35 households already mentioned. This group included 43 paralytic patients from whom poliomyelitis virus was isolated in 79.0%. Among 50 nonparalytic patients, 52.0% had virus in the stool. In the group of symptomatic household contacts 57.0% had virus in their stools, and in the 113 asymptomatic household contacts only 34.0% showed the presence of poliomyelitis in the stool. Stools obtained from persons 15-21 days after onset of symptoms had as high an incidence of virus as at an earlier time, but after 21 days the percentage of positive stool virus isolations dropped sharply, even though some were positive for as long as 42 days. Other features of this study indicated that one-third of the persons having household contact with a clinically diagnosed poliomyelitis patient had the virus in their stool and that the virus-carrier rate was considerably higher among household contacts who had symptoms indicating illness. This was particularly notable in the latter group exposed to a paralytic patient, especially if they were under 10 years of age. It is of interest that 80.0% of all virus carriers were free of symptoms of illness. Gamma globulin administered to household contacts seemed not to influence the appearance of virus in fecal specimens.

The American Journal of Medicine, New York

20, No. 4 (April) 1956

* Serologic Reactions in Rheumatoid Arthritis. Wallace Epstein and Charles Ragan.—p. 487.

* The Hemagglutination Test for Rheumatoid Arthritis: III. Clinical Evaluation of the Sheep Erythrocyte Agglutination (S. E. A.) Test and the Gamma Globulin (F II) Tests. Abraham S. Jacobson, William H. Kammerer, Julius Wolf, Wallace V. Epstein, and George Heller.—p. 490.

* Agglutination and Inhibition by Serum Globulin in the Sensitized Sheep Cell Agglutination Reaction in Rheumatoid Arthritis. Morris Ziff, Patricia Brown, Joseph Lospalluto, Jacques Badin, and Currier McEwen.—p. 500.

Synovial Specimens Obtained by Knee Joint Punch Biopsy: Histologic Study in Joint Diseases. Henry A. Zevely, A. James French, William M. Mikkelsen, and Ivan F. Duff.—p. 510.

Diagnostic Methods for Allergic Diseases. William B. Sherman.—p. 603.

Studies on a Patient with Severe Hyperinsulinism Treated with Cortisone for Three Years. Herbert Gershberg and Elaine P. Ralli.—p. 631.

Infectious Mononucleosis of the Central Nervous System: Demonstration of Atypical Lymphocytes in the Cerebrospinal Fluid. Leo E. Hollister, George H. Houck, and William A. Dunlap.—p. 643.

20, No. 5 (May) 1956

Pathways of Iodine Metabolism. Solomon A. Berson.—p. 653.

Recent Progress in the Physiology and Biochemistry of Thyroid Hormones. Raymond Michel.—p. 670.

Physiologic Concepts in the Diagnosis and Treatment of Graves' Disease. Brown M. Dobyns.—p. 684.

Physiologic Considerations in the Genesis and Management of Nodular Goiter. Selwyn Taylor.—p. 698.

Physiologic Concepts in the Genesis and Management of Thyroid Tumors. Martin Sonenberg.—p. 710.

* The Role of Radioactive Iodine in the Diagnosis of Thyroid Disease. J. E. Rall.—p. 719.

Physiology and Treatment of Myxedema. Samuel P. Asper Jr. and John G. Wiswell.—p. 732.

Pulmonary Valvular Stenosis with Intact Ventricular Septum: Results of the Brock Type Valvulotomy. C. Walton Lillehei, Paul Winchell, Paul Adams, Ivan Baronofsky, Forrest Adams, and Richard L. Varco.—p. 756.

Bronchial Asthma: Francis C. Lowell.—p. 778.

Potassium Depletion by Enemas. Marcelle F. Dunning and Fred Plum.—p. 789.

Serologic Reactions in Rheumatoid Arthritis; The Hemagglutination Test for Rheumatoid Arthritis: III. Clinical Evaluation of the Sheep Erythrocyte Agglutination (S. E. A.) Test and the Gamma Globulin (F II) Tests; Agglutination and Inhibition by Serum Globulin in the Sensitized Sheep Cell Agglutination Reaction in Rheumatoid Arthritis.—This series of three papers provides a review of the various serologic tests used in rheumatoid arthritis and also demonstrates the efforts now under way to improve the specificity of these tests. Three serologic test systems have been investigated: the streptococcic agglutination test (S. A.), the sensitized sheep cell test (S. S. C.), and the Cohn fraction II system test (F II). In each test a substance (the reactor) found only in the water insoluble or euglobulin fraction of the serum of patients with rheumatoid arthritis reacts with a "reactant" to cause agglutination of sheep erythrocytes. In the case of the S. A. test the reactant is a pseudoglobulin found in the serum of normal adults; for the S. S. C. test, the reactant is rabbit anti-sheep erythrocyte serum, while the reactant for the F II test lies within the gamma globulin of certain human serums. A third factor in these tests is an inhibitor found in the euglobulin and euglobulin

supernatant of nonrheumatoid sera but only in the supernatant of rheumatoid sera. Upon this knowledge of the distribution of the reactor and the inhibitor there have been based the modifications aimed to increase the specificity of the tests.

As reported in the paper by Jacobsen and associates, the unmodified S. S. C. test gave agglutination in 62% of 331 patients with "peripheral" rheumatoid arthritis while the F II test was positive in 69% of 180 rheumatoids. In 32 of 46 sera both tests were positive. In contrast the sera of 516 nonarthritic patients gave agglutination in 3% with the S. S. C. test and 2% with the F II test. The sera from patients with disorders possibly resembling rheumatoid arthritis (such things as rheumatic fever, disseminated lupus erythematosis, or traumatic arthritis) resulted in agglutination in less than 8.7% by either test. Both the paper of Jacobsen and associates and that of Ziff and his colleagues pointed out that sera of patients with rheumatoid spondylitis or with psoriasis and arthritis result in far less frequent agglutination than do the sera of patients with "peripheral" rheumatoid arthritis. To Ziff, this fact suggests that there is a basic difference in the underlying mechanism of "peripheral" rheumatoid arthritis as compared with the other two disorders.

In an attempt to increase the accuracy of the S. S. C. test, Ziff and co-workers repeated the test using euglobulin instead of whole sera. By this means, the per cent of positive results with rheumatoid sera increased to 92% while the control sera still showed agglutination in only 2%. Further value was obtained by testing for the inhibitor using euglobulins. The pattern of results using rheumatoid sera then showed agglutination in 65% with whole serum and in 95% with euglobulin and no inhibition by euglobulin. In contrast, blood from control patients demonstrated inhibition and no agglutination using euglobulin with occasional agglutination using whole serum.

The results on these tests showed some increase in per cent positive when done on patients with severer rheumatoid arthritis or with the disease in later stages. Likewise the longer the duration of the arthritis the more likely the tests will be positive; however, using the euglobulin modification Ziff obtained positive results in all 10 patients studied within six months of the onset of the disease. With regard to the use of these tests in juvenile rheumatoid arthritis, most reports have been discouraging. Nevertheless, using the euglobulin modification Ziff's group obtained positive results in four out of seven sera from juvenile rheumatoids.

The Role of Radioactive Iodine in the Diagnosis of Thyroid Disease.—This paper, one of an excellent symposium on the pathologic physiology of thyroid disease, can be used to summarize present theories concerning the pathways in the production of thyroid hormone and some of the methods of studying these steps. Iodide, absorbed by the intestines, is "trapped" and concentrated by the thyroid gland. The thyroid plasma iodide clearance of I^{131} or the 1- and 24-hour I^{131} uptakes measure the "trapping" ability as it is influenced by dietary iodide, renal iodide clearance, and thyroid blood flow. On the whole, these tests are satisfactory measures of thyroid status.

The second step of thyroid hormone production is the "organification" of iodide or the oxidation of iodide into organic iodine which combines with tyrosine to form, in turn, monoiodotyrosine, diiodotyrosine, and finally thyroxine. Failure of organification occurs congenitally in certain familial cretins, while blocking of this step is the mechanism of action of thiouracil and mercaptoimidazole. The amount of I^{131} remaining one hour after thiocyanate has cleared the thyroid of all iodine not yet organically bound provides a measure of thyroid organification.

Within the thyroid, the hormone is stored in the thyroglobulin. Abnormalities of thyroglobulin have not yet been described with certainty; however, it is thought one form of congenital goiter may be due to an abnormality in the breakdown of thyroglobulin, such that diiodotyrosine is not deiodinated and accordingly appears in the blood stream. This disorder can be demonstrated by paper chromatography. Tests of the actual rate of thyroid hormone secretion remain complex and inaccurate. The rate of degradation of the hormone in the tissues may be ascertained by testing the amount of protein-bound I^{131} persisting 15-20 days after giving labelled thyroxine. In Graves' disease and in nephrosis, such degradation appears increased. In the blood stream thyroxine is carried bound to an alpha globulin. This bond results in a slow release of thyroxine, a fact which may explain the slower action of thyroxine or desiccated

thyroid as compared with triiodothyronine. This, as well as other evidence, suggests that triiodothyronine is the final active form of the thyroid hormone. Tables of the normal and abnormal values found with these various tests are provided.

American Journal of Pathology, Ann Arbor, Mich.

32:663-870 (July-Aug.) 1956

* Visceral Larval Migrans, With a Case Report. John H. Dent, Robert L. Nichols, Paul C. Beaver, G. M. Carrera, and R. J. Staggers.—p. 777.

Visceral Larval Migrans, With a Case Report.—A 19-month-old boy was hospitalized because of fever, abdominal distention, and malaise. Although the liver was enlarged, there was no jaundice. The total leucocyte count varied between 30,000 and 63,000/cu. mm., and there was as much as a 60% eosinophilia. Febrile agglutination tests were negative, but the heterophile antibody titer was 1:7168. A liver biopsy obtained at laparotomy contained numerous granulomata in which there were T. canis larvae. The patient was treated supportively and with antibiotics; he improved greatly during the next month and a half. However, he then suddenly developed chills, fever, and jaundice. Within days he became comatose and died from what appeared to be overwhelming hepatitis. He had received several transfusions at the time of the biopsy.

At postmortem examination numerous granulomata containing nematode larvae were present in the heart, lungs, liver, kidney, intestines, mesenteric lymph nodes, brain, and spinal cord. In addition, there was diffuse and complete hepatocellular necrosis consistent with severe homologous serum hepatitis, in association with an inflammatory cell infiltrate. Motile larvae were recovered from pepsinized fresh tissue, and were morphologically identified; there were 60 larvae per gram of liver, 5 larvae per gram of muscle, and 3-5 larvae per gram of brain. Granulomata were most frequent in the liver and lungs, although not all contained identifiable larvae. It was assumed that the presence of larvae within the central nervous system might account for the neurological manifestations.

The American Review of Tuberculosis and Pulmonary Diseases, New York

74, No. 1 (July) 1956

The Action of Cortisone on Corneal Tuberculosis Studied with the Phase Contrast Microscope. J. M. Robson and K. A. Didcock.—p. 1.
The Effects of Isoniazid Treatment on the Tuberculin Reaction and on the Healing of BCG Vaccine-Induced Ulcers. Joseph D. Aronson, Helen C. Taylor, and Daniel L. Kirk.—p. 7.
* Serum Gamma Globulin in Childhood Tuberculosis. Charlotte Marker Zitrin, Edith M. Lincoln, Abraham Saifer, and Stephanie Lewokicz.—p. 15.
The Antituberculous Activity of Thioethyl Compounds. Morris Solotorovsky, Seymour Winsten, Elliott J. Ironson, and Horace D. Brown.—p. 59.
Enumeration of Viable Tubercle Bacilli. Maurice S. Tarshis and Sanford S. Elberg.—p. 84.
The Presence of Lupus Erythematosus Cells in Miliary Tuberculosis. H. W. Haverland.—p. 112.
Editorial: Chemoprophylaxis, Immunity and Prevention in Tuberculosis. Rene J. Dubos.—p. 117.
Cycloserine Therapy in Tuberculosis in Humans. W. Lester Jr. and others.—p. 121.
Clinical, Bacteriologic, and Pharmacologic Observations upon Cycloserine. A. D. Renzetti and others.—p. 128.
Tuberculous Adenitis. K. Butler.—p. 136.
Incidence of Tuberculous Infection in Infancy. E. L. Kendig Jr.—p. 149.

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* A Pilot Study of Cycloserine Toxicity: A United States Public Health Service Cooperative Clinical Investigation.—p. 196.
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Correlation of in Vitro Susceptibility of Tubercle Bacilli in Patients with Miliary and Meningeal Tuberculosis with Their Response to Therapy. Hattie E. Alexander, Douglas S. Damrosch, and Catherine Ellis.—p. 232.
The Course and Prognosis of Endobronchial Tuberculosis in Children. Edith M. Lincoln, Leonard C. Harris, Somchai Bovornkitti, and Rosario Carretero.—p. 246.
Experiences with Intra- and Extraluminal Bronchial Tuberculous Lesions. Robert H. High and Waldo E. Nelson.—p. 256.
Bronchoscopy in Primary Tuberculosis of Childhood. Herman I. Laff, Maurichio Goldberg, and William F. Russell Jr.—p. 267.
Views in Perspective. Bela Schick.—p. 297.

Serum Gamma Globulin in Childhood Tuberculosis.—The authors studied 18 children, with various forms of tuberculosis. Gamma globulin was determined by two methods: the colorimetric flocculation-Ninhydrin procedure of Saifer and co-workers and the zinc-sulfate-turbidity method of Kunkel. It appears that there is a fairly good correlation between the two methods.

Results of the study suggest that serum gamma globulin values in children with tuberculosis, particularly if serial determinations are made, may be of aid in the diagnosis and prognosis of this disease.

A Pilot Study of Cycloserine Toxicity: A United States Public Health Service Cooperative Clinical Investigation.—A control study on the toxic effects of cycloserine was conducted in six hospitals on 141 tuberculous patients in such a way that neither patients nor physicians knew whether a particular patient was receiving drug or placebo.

During the 12-week course, toxic reactions severe enough to necessitate departure from the assigned regimen occurred in 18 or 115 patients who received cycloserine and in none of the placebo patients. Eight patients had convulsions; two, mental disorders; three, motor disorders; one, somnolence; three, dizziness; and one, fever and chills.

Cycloserine possessed a measure of therapeutic effectiveness, as indicated by absence of roentgenographic deterioration and by a moderately high bacteriologic rate. The excellence of other available antimicrobial combinations and the toxicity of cycloserine will probably preclude its use for initial treatment. Further studies will be necessary to determine its usefulness in small doses, either alone or in combined therapy, for patients who have failed to respond adequately to combinations of isoniazid, streptomycin, and PAS.

Vaccination Against Tuberculosis: Clinical Aspects.—BCG produces a specific immunity that increases the resistance to any virulent tuberculous infection. The author produces some experimental evidence to support this thesis.

At present time, BCG vaccination in the form of mass vaccination is important in those countries where primary infections develop early in childhood and manifest forms of primary tuberculosis and early postprimary disease are common. In countries with late primary infections and satisfactory nonspecific resistance, the great majority of BCG vaccinations will never exert a protective influence during childhood.

BCG vaccination should always be carried out in those cases in which danger of exposure is particularly marked, e. g., in children living in tuberculous surroundings or among those occupationally exposed to tuberculosis, such as medical students, nurses, or the staff of a

sanatorium or other hospital or institution to which people with tuberculous disease may be admitted.

Systematic Treatment of Primary Tuberculosis.—The author stresses the importance of early diagnosis and prompt institution of treatment. He makes special reference to those who are symptom-free.

Preliminary findings, based on 18 months study of about 3000 patients and controls, indicate the value of treatment, especially in the response of lung opacities due to tuberculous disease and to a lesser extent in the response of adenitis and atelectasis.

Routine treatment consists of INH, 10 mg. per kilogram body weight, with maximum daily dosage of 400 mg., and PAS, 300 mg. per kilogram body weight. Therapy is continued for six to eight months. Streptomycin is held in reserve.

Cortisone should be used in the treatment of severe forms with high and protracted fever, primary and postprimary serofibrinous pleurisy, and distressing disorders related to large mediastinal glands.

Annals of Internal Medicine, Lancaster, Pa.

44, No. 3 (March) 1956

Discoid Lupus Erythematosus: An Analysis of Its Systemic Manifestations. Edmund L. DuBois and Stuart Martel.—p. 482.

Evaluation of Three Diagnostic Procedures for Systemic Lupus Erythematosus. John R. Haserick.—p. 497.

Essential of Pulmonary Hypertension: A Report of Clinical-Physiologic Studies in Three Patients, with Death Following Catheterization of the Heart. H. Schafer, J. M. Blain, R. Ceballos, and R. J. Bing.—p. 505.

Treatment of Toxoplasmosis with Pyrimethamine (Daraprim) and Triple Sulfonamide. R. F. Wettingfeld, John Rowe, and Don E. Eyles.—p. 557.

Adult Toxoplasmosis: Report of a Case Due to Laboratory Infection. Josiah Brown and Leon Jacobs.—p. 565.

Glycine and Sodium Glucoronate in the Management of Convulsions Due to Hydrazides. Sol Katz, Abe Gimble, Georges McCormick, and Benjamin Prescott.—p. 576.

Editorial: Association of Irradiation with Neoplasia in Children and Adolescents.—p. 579.

Essential Pulmonary Hypertension: A Report of Clinical-Physiologic Studies in Three Patients, with Death Following Catheterization of the Heart.—Three patients, ages 7, 14, and 33, died immediately after heart catheterization. All had very high pulmonary artery, right ventricular, and right atrial pressures; and in two from whom oxygen contents were obtained there was no evidence of a left to right shunt. The two children were autopsied and found to have thickening of the intima and media of the pulmonary arterioles with complete occlusion in some vessels. In the 7-year-old child there were also perivascular inflammation, thickening of the septa, and marked arteriosclerotic changes in the larger arteries. There were no congenital or rheumatic defects of the heart or great vessels in either case.

The most prominent symptoms in these, as in other reported cases, were syncope on exertion and dyspnea. Experimental work in animals suggests that they are produced by a reflex which is initiated by distension of the pulmonary vessels. All three had systolic murmurs and accentuation of the pulmonic second sound; two had diastolic murmurs as well. It is therefore easy to mistake this disease for congenital or rheumatic heart disease. Electrocardiograms showed right axis deviation and right ventricular hypertrophy; while enlargement of the heart as a whole, and of the right ventricle, main pulmonary artery, and perihilar shadows with decreased peripheral pulmonary vascular markings was seen on x-ray examination.

These deaths, the only fatalities in over 900 catheterizations at the Medical College of Alabama, were all associated with arrhythemias although the catheter had been withdrawn before their onset. Other usually harmless procedures, including injection of Decholin for the determination of circulation time and barbiturate anesthesia, have also been fatal in patients with essential hypertension whose lives are therefore continually menaced.

MISCELLANEOUS

Diseases of Blood, Heart and Blood Vessels, and Spleen

DIFFERENTIATION OF FACTOR 3 AND FACTOR 4 OF THE PLATELETS IN A PATIENT WITH A HEMORRHAGIC DIATHESIS. S. VAN CREVELD and H. A. VEDER, Nederl. tijdschr. geneesk. 99: 2882 (Sept. 24) 1955.

Description of a case of hemorrhagic diathesis in a child, which was characterized by a shortage of several platelet factors, the number of platelets being normal. Since the heparin neutralizing capacity of the platelets was normal whereas their thromboplastic capacity was abnormal, we must conclude that factor 3 of the platelets, described by the authors, combines two different functions: a thromboplastic factor, which remains indicated by the name factor 3, and a factor 4, which neutralizes heparin.

VAN CREVELD, Amsterdam

FORMATION OF THROMBOPLASTIN, IN USING A SUSPENSION OF PLATELETS AND A SO-CALLED PLATELET-SUBSTITUTE RESPECTIVELY. H. BAKER, G. J. ADDENS, J. GEERLING, A. VAN 'T LAAR, and N. A. MEURSING, Nederl. tijdschr. geneesk. 99:3688 (Dec. 3) 1955.

The formation of thromboplastin under various conditions was studied in vitro by means of the thromboplastin generation test of Biggs and Douglas.

The authors found that a suspension of platelets could be used for this test even after many months if it was stored in a frozen condition and was not defrosted too often. The results obtained with such a platelet suspension and with a "platelet substitute" corresponded under varying conditions.

VAN CREVELD, Amsterdam

CHEMOPROPHYLAXIS OF RHEUMATIC FEVER IN CHILDREN. S. VAN CREVELD, M. G. STRONK, and M. R. H. STOPPELMAN, Nederl. tijdschr. geneesk. 99:614 (Feb. 26) 1955.

This article reports on the experiences of the pediatric clinic of the University of Amsterdam in the chemoprophylaxis of acute rheumatic fever in childhood during the period of April, 1948, till July 1, 1954. During this period 246 patients were checked regularly for one year or more; 172 children received chemoprophylaxis. In the group of children with regular chemoprophylaxis the authors saw 6 relapses in 186 "person years"; in the group of children who did not take sulfadiazine regularly there were 12 relapses in 77 "person years." Eight relapses occurred in periods when no chemoprophylaxis was given.

VAN CREVELD, Amsterdam

THE ISOLATION OF THE ANTI-HEMOPHILIC FACTOR FROM HUMAN PLASMA. S. VAN CREVELD, P. G. HOORWEG, G. J. H. DEN OTTOLANDER and H. A. VEDER, Amsterdam (the Netherlands), Nederl. tijdschr. geneesk. 99:2269 (July 30) 1955.

Many investigators who accept that in hemophilia a clotting-promoting factor is lacking which is present in normal plasma have tried to isolate this factor. In 1935, Bendien and van Creveld for this purpose used the method of precipitation by salting-out and the method in which the clotting promoting substance was prepared by tenfold dilution of plasma with distilled water followed by acidification till pH 5.4 by 0.1 N acetic acid. Also the principle of adsorption and elution was used for this purpose by the authors mentioned and in this way already in 1936 an active product was obtained which contained less than 1 pro mille of protein.

In this article the authors describe how they succeeded in different other ways to get active preparations of the antihemophilic factor which are relatively poor in protein. However, the problem remains provisionally unsolved whether or not the antihemophilic factor itself is a protein.

VAN CREVELD, Amsterdam

HEMOLYTIC-UREMIC SYNDROME: BILATERAL RENAL CORTICAL NECROSIS WITH ACUTE ACQUIRED HEMOLYTIC ANEMIAS. C. GASSER, E. GAUTIER, ANNEMARIE STECK, R. E. SIEBENMANN and R. OECHSLIN, Schweiz. med. Wchnschr. 85:905-909, 1955.

Four girls and one boy aged 2 to 14 months and 7 years were seen on account of an acute acquired hemolytic anemia together with or followed by severe renal insufficiency ending fatally

in 3-12 days. Thrombocytopenic purpura and cerebral symptoms also existed. The hemolytic-uremic syndrome followed lighter or severer infections. On postmortem examination bilateral necrosis of the renal cortex and glomeruli were present in all cases. In one case, a 7-months-old girl, a thrombotic microangiopathy (Symmers) was found.

MECHANICAL DRAINAGE of the EDEMA of the skin. H. Schaeffer, Deutsche. med. Wchnschr. 80:1426-1429, 1955.

A new drainage tube is described which offers advantages over previous ones. Since the danger of infection is reduced very much by the antibiotics the drainage of skin edemas properly conducted, as outlined, can be very effective in cases of high degree of edema of the skin as in cardiac insufficiency and in nephrosis. It was also possible to influence ascites and stasis of lungs and liver. Control by the determination of the serum electrolytes is necessary.

FREQUENCY OF HAEMOPHILIA A AND B. G. J. H. DEN OTTOLANDER and P. G. HOORWEG, Nederl. tijdschr. geneesk. 99:2037 (June) 1955.

The history of research in differentiation between hemophilia A (the "classical" condition) and hemophilia B (Christmas disease) is briefly sketched. Clinically these conditions cannot be differentiated, but a chemically different plasma-factor is absent in each of them. In 129 patients with hemophilia the differential diagnosis between A and B was made by laboratory methods (i.e., addition of antihemophilia factor, the "thromboplastin generation test" according to *Biggs* and *Douglas*, and crossing with plasma of known patients with hemophilia A resp. B). Hemophilia B proved to be present in 8% of all cases. This is approximately the same percentage as has been found in Western Europe and U.S.A. (according to most publications mentioned by the authors). The total number of hemophiliacs in the Netherlands is estimated at about 1000, i.e., 0.1 pro mille of the total population, one-third of these being cases of sporadic hemophilia. The total number of cases will probably increase and the number of sporadic cases decrease because of the fact that nowadays male hemophiliacs reach adolescence oftener. The differential diagnosis between A and B is important for the therapy, e.g., because A patients must be treated with fresh blood (the antihemophilic factor being thermolabile) and B patients do well on blood from a bloodbank (ac-factor being thermostabile).

VAN CREVELD, Amsterdam

SOME INVESTIGATIONS CONCERNING THE ABNORMAL HAEMOGLOBIN C. T. H. J. HUISMAN, P. C. VAN DER SCHAAF, AND A. VAN DER SAR. Nederl. tijdschr. geneesk. 99:2284 (July 30) 1955.

The article gives a description of one practically white and of one Negro family in the Dutch West Indies (Curacao) in which both homozygous and heterozygous forms of hemoglobin-C illness were found.

The properties of hemoglobin C as well as the differences between this and other kinds of hemoglobins are extensively studied and described.

With the aid of five different methods it was possible to prove that in the homozygous form of the disease only hemoglobin C is occurring.

VAN CREVELD, Amsterdam

MYELOSIS ERYTHRAEMICA (DR. GUGLIELMO) IN CHILDREN. KHO LIEN KENG, TE BEH SIANG and GAMBIRO, Maandschr. kindergeneesk. 23:6 (Jan.) 1955.

Description of three cases of myelosis erythremica in three Asiatic boys of 6, 10, and 5½ months, respectively.

The symptoms were grave normocytic, normochromatic, or hypochromatic anemia, fever, loss of appetite, hemorrhagic diathesis (in two cases), thrombopenia, hepatosplenomegaly, adenopathy, proliferations of nucleated erythrocytes in bone marrow, liver, and spleen, and resistance against all therapy. There was anisocytosis, poikilocytosis, and polychromasia. There were nearly no "target" cells. The number of reticulocytes was sufficient and sometimes too high. The resistance of the red cells against sodium chlorine in two cases was normal and in one case too high. Hemolysis was never seen, neither was jaundice. The symptoms resemble those in leukemia, but the differnce is that in leukemia we find young cells from the white series in the blood and the organs, and in myelosis erythremica an increase of nucleated erythrocytes. In erythroleukemia we find myeloid and erythroid tissue in the organs, and young cells from the white and red series in the peripheric blood. One of the most important findings

in leukemia, erythroleukemia, and myelosis erythraemica is the absence of or the presence of only very few megakaryocytes.

The etiology is unknown as in leukemia. In a newborn child the disease should be differentiated from erythroblastosis fetalis. When the children are older we must differentiate from hemolytic anemia, lues, tuberculosis, and rickets.

In Indonesia, where malaria is a very common disease, we have to differentiate also from chronic malaria with hyperplastic bone marrow.

The first case described in this article, occurred acutely, the second peracutely and the third became chronic, all three ending fatally.

S. van Creveld, Amsterdam (the Netherlands)

Hemorrhagic Diathesis by Lack of the PTA-Factor. S. van Creveld and H. A. Veder, Maandschr. kindergeneesk. 23:317 (Sept.) 1955.

Reference is made to a new hemorrhagic disease, resembling hemophilia, caused by a lack of an as yet unknown thromboplastic factor, called plasma thromboplastin antecedent (PTA), which was first described by Rosenthal and others in 1953.

A patient is described with a hemorrhagic diathesis which was demonstrated to be caused by a shortage of the coagulation factor PTA. This shortage was not constantly present.

S. van Creveld, Amsterdam

The Mechanical Fragility of Erythrocytes. S. E. Bos, Maandschr. kindergeneesk. 23:335 (Oct.) 1955.

A method of applying the mechanical fragility test for erythrocytes is given. It is a modification of the technique of Goldbloom. This rather simple method is tested in 63 normal adults, 10 normal newborn infants, and 4 cases of hemolytic disease of newborn, 3 of which were due to a Rhesus incomptability and 1 to ABO incomptability, 10 cases of acholuric jaundice and several cases of acquired hemolytic anemia. The mechanical fragility test proved to be a simple test of great diagnostic value. It gives more information on the real fragility of the erythrocytes in vivo than does the osmotic fragility test. The osmotic fragility test only increases in the presence of spherocytes, whereas the mechanical fragility test corresponds with the normal destruction of erythrocytes in vivo.

S. van Creveld, Amsterdam

Clotting Factors in Morbus Haemolyticus Neonatorum. J. I. de Bruijne and S. van Creveld, Nederl. tijdschr. geneesk. 99:3875 (Dec. 24.) 1955.

In 27 children suffering from hemolytic disease of the newborn a number of clotting factors were determined before and in a restricted number of cases also after an exchange transfusion. In an important part of the cases before the exchange transfusion, next to the physiological hypoprothrombinemia a diminution of the proaccelerin (factor V) was found. Some days after the exchange transfusion this diminution had totally or nearly totally disappeared in the cases examined.

van Creveld, Amsterdam

Diseases of Nose, Throat, and Ear

The School Adjustment of Children with Minimal Hearing Loss. Lyle Gordon Reynolds, J. Speech & Hearing Disorders 20:380-384 (Dec.) 1955.

Thirty-six hard-of-hearing students in the seventh, eighth, and ninth grades, demonstrating a minimum hearing loss or better of 15 decibels at each 512, 1024, and 2048 cycles, or 20 decibels loss at any 2 of these frequencies, or 25 decibels at any loss, were studied for their adjustment and school environment by the California Achievement Test, California Test of Personality, and rating by various teachers. These 36 hard-of-hearing children were studied by the matched-pair method with normal children. In this study the children with minimal hearing loss adjusted their school environment as favorably as their normally hearing partners.

Palmer, Wichita, Kan.

Diseases of Lungs, Pleura and Mediastinum

Contrasting Roentgenographic Pulmonary Patterns of the Hyaline Membrane and Fetal Aspiration Syndromes. H. G. Peterson Jr. and M. E. Pendleton, A. J. Roentgenol. 74:800 (Nov.) 1955.

This is an excellent article giving considerable material for thought. It consists of a study of 147 infants with respiratory distress. These children have all been studied from a radiographic and a clinical standpoint.

The radiographic findings in the chest were divided into two major catagories: those having a finely reticulogranular pattern and those having a coarse irregular pattern. The finely reticulogranular pattern had a very high correlation in children with hyaline membrane disease, whereas the coarse and irregular pattern was correlated highly with those children who had fetal aspiration syndromes, and particularly was true in the postmature infant.

The possibility of inflammatory infiltration or focal hemorrhage could not be excluded as pathologically these conditions were found to occur in the children with either type of lung findings. The article is recommended and the differentiation is one which is valuable in the study and care of newborn infants with respiratory distress.

ALTMAN, Miami, Fla.

PATHOLOGIC FEATURES OF RESPIRATORY DISTRESS SYNDROMES IN NEWBORN INFANTS. BENJAMIN H. LANDING, A. J. Roentgenol. 74:796-799 (Nov.) 1955.

This is an article written to summarize findings of 178 unselected newborn autopsies performed by the Department of Pathology of the Children's Medical Center in Boston. Of these children 152 or 85% were found to have pulmonary lesions at autopsy. Of the 85% who had pulmonary disease the greatest majority had one significant lesion and four other minor lung conditions. Conditions listed consist of atelectasis, emphysema, hemorrhage, interstitial emphysema, amniotic material aspiration, immaturity, edema, hyaline membrane disease, or pneumonia.

The article stresses the fact that in view of the combined diseases of so many of these children it is difficult for the roentgenologist to say with certainty that any one child has a specific cause for apneumatosis. This term is used to refer to decreased pulmonary aeration. In addition, there is a brief mention of the findings of hyaline membrane disease and the causes and clinical course.

ALTMAN, Miami, Fla.

SEQUESTRATION OF THE LUNG. S. E. Bos, Nederl. tijdschr. geneesk. 99:2203 (July 23) 1955.

In a 3-year-old girl suffering since the first year of life from recurrent infections of the respiratory tract, an opacity with cavities in the lower part of the right lung was present for at least six months. At bronchography there was no filling with Lipiodol. Only once the child coughed suddenly purulent sputum. The diagnosis of intralobar sequestration was suspected. At operation a cystic mass was found, one large artery leading from the diaphragm toward it. After removal of the cystic mass the patient was cured. The pathologic findings confirmed the diagnosis.

VAN CREVELD, Amsterdam

ASTHMA AND THE ORDER OF BIRTH. G. J. HUET, Nederl. tijdschr. geneesk. 99:3501 (Nov.) 1955.

It was demonstrated that asthma occurs significantly more frequent in the firstborn than in the lastborn child. This seems to be interrelated with the loss of the temporary position as the only child and therefore constitutes an objective criterion in testing the possible influence of certain psychogenic factors. Further investigations showed that the first child's "predisposition" is only involved in mild forms of asthma; it is lacking in cases of severe and frequent attacks. Two types of asthma should therefore be distinguished, in this respect, in children.

VAN CREVELD, Amsterdam

LUNG INFECTION BY NOCARDIA. W. J. STEYLING, Maandschr. kindergeneesk. 23:438 (Dec.) 1955.

Description of a case of obstructive pneumonia with bilateral hilum glandular swelling, with negative tuberculin test. Bronchoscopy was performed, but no foreign body was found. Bronchial secretion was cultured. Nocardia astereoideus—an aerobic Actinomycetaceae—was found. The patient was treated with penicillin and streptomycin and cured.

VAN CREVELD, Amsterdam

Diseases of Gastrointestinal Tract, Liver and Peritoneum

CONGENITAL RECTO-URETHRAL FISTULAE. W. A. MOONEN and M. M. AUSEMS, Nederl. tijdschr. geneesk. 99:2595, (Aug. 27.) 1955.

Rectourethral fistulae should be regarded as complications of atresia ani. It is important to think about them in a child with atresia ani.

Two advisable operations for this condition are mentioned in the literature, viz., immediate abdominoperineal technique and delayed sacral surgery.

The authors treated three children whose atresia ani had been corrected, while the fistulae had been ignored. These children were in an extremely unfavorable condition due to recurrent infections of the urinary tracts. Simple perineal surgery effected a complete recovery of their general condition. The urine and intestines were sterilized with 0.5 gm. Aureomycin a day, from four days before the operation till four days after the operation.

VAN CREVELD, Amsterdam

A CASE OF ATYPICAL CIRRHOSIS OF THE LIVER (LAENNEC'S CIRRHOSIS) IN A CHILD. D. P. R. KEIZER, Nederl. tijdschr. geneesk. 99:2301 (Aug.) 1955.

A boy aged 5 born in a healthy peasant family without any hereditary anomalies developed Laennec's cirrhosis of the liver. Ascites and jaundice set in rather acutely after one and one-half to two years. In about a month acute necrosis of the liver had developed and caused the child's death. At autopsy the pathologist considered the process to have been in progress for about one and one-half to two years.

Although no symptoms of acute poisoning could be found, the author suspects affection of the liver by frequent and prolonged contact with insecticides which had been stored in a barn for years.

About 8 months after the death of this boy his 10-year-old brother was admitted to the clinic with a history of nausea and vomiting, dark urine, and jaundiced sclerae since 3 weeks. The diagnosis again was Laennec's cirrhosis of the liver. The only surprising finding was an increased excretion of Hg in the urine. Treatment with methionine and Aureomycin during two weeks had no effect, BAL for 10 days did have some. A porta-cava shunt will be made. As the urine of this child was completely normal at control during his brother's disease, a familiary disposition is not likely and suspicion of intoxication is maintained. The mother is pregnant with a third child which will be sent for investigation as soon as possible after birth.

VAN CREVELD, Amsterdam

FOLKLORE REMEDY (CANADA FLEABANE) FOR SOYBEAN DIARRHEA: "MULE TAIL TEA." JOHNNY A. BLUE, J. Allergy 26:425 (Sept.) 1955.

The author relates his introduction to the use of this herb in the treatment of diarrhea while on a fishing trip. He subsequently used it successfully in the treatment of diarrhea caused at times by soybean formulae. He makes a tea of the herb and uses it as the water in making the soybean formula.

The author's conclusions have some merit.

"Sometimes simple remedies, even though folklore in origin, with a scientific background and investigations, can prove very helpful in aggravating and difficult conditions.

"It is well to remember the old and proved drugs and remedies and not be too prone to discard them and climb onto the proverbial bandwagon of new drugs."

HOYER, Cincinnati

Nervous Diseases

DECEREBRATION SYNDROME AFTER ETHER-NARCOSIS. V. W. D. SCHENK, Maandschr. kindergeneesk. 23:19 (Jan.) 1955.

A case is reported of a child 1 year 8 months old who showed a complete decerebration after ether narcosis for a hernia operation. Fifteen days before the operation this child had suffered from chicken pox. The decerebration remained, and the child had to be artificially fed for six years because she could not swallow. She was laying passive in bed and did not react at all. Six years after the operation the child died. At autopsy lesions were found in the cerebral and cerebellar hemispheres. Besides atrophy of the brain mantle thére was found a status marmoratus of nucleus caudatus, putamen, and of large parts of the thalamus opticus.

Below the mesenphalic level only the cerebellar cortex showed important destruction. The (possible) relation of the chicken pox, ether narcosis, and operation are discussed.

VAN CREVELD, Amsterdam

A CONTRIBUTION TO THE STUDY OF REFLEXES IN THE NEWBORN AND PREMATURE INFANT—VERTEBRAL FRICTION REFLEX. M. CARBONELL JUANICO AND PEREZ DEL PULGAR MARX, Rev. españ. Pediat. 11:317-322 (May-June) 1955.

The authors call this procedure the digital vertebral friction reflex complex, and it brings out a series of responses in a regular sequence. The nude baby is placed in the prone position and should be at rest and not crying. Alternate position is prone on the examiner's left hand with head and extremities pendulous. The right index finger of the examiner is used to produce a light friction along the vertebra from the coccyx to the neck.

Nine different responses can be obtained, all due to excitation of bulbo-mesencephalico-medular centers. In a child with injury to these subcortical areas the response will be quite atypical.

The appearance of this reflex complex is at birth to 24 hours. Heavy anesthesia of the mother may prolong its appearance. It persists several weeks and disappears in a regular order. Its failure to disappear within a few weeks should make one suspect nervous-system immaturity.

MARY ALLEN, Santa Fe, N. M.

THE CLINICAL POSITION OF PYKNOLEPSY. D. JANZ. Deutsche. med. wchnschr. 80:1392-1400, 1955.

A study of 163 pertinent cases of pyknolepsy from two institutions was extended over a number of years; of these only 16% healed spontaneously, that is they were free from attacks, 10-14 years after onset, at least for 2 years. Another 31% remained pyknoleptic while in 53% grand mal attacks supervened. This occurred on the average after 5-6 years but as late as 22 years later. Spontaneous healing of pyknolepsy is not the rule, as had been stated, but rather the exception. The age of onset extends from the 4th to the 14th year of life. The great majority starts at 6 to 8 years of age. Pure absences without any motor or sensory symptoms occur in 13%. They also can occur in minimal petit mal attacks. In other cases some motor manifestations are seen. It is concluded that pyknoleptic seizures can not be differentiated electroencephalographically from petit mal of a given age group. They are regarded as rudimentary forms of any kind of petit mal. For treatment Tridione or Paradione are recommended.

THE ELECTROENCEPHALOGRAM IN RETROLENTAL FIBROPLASIA. E. L. GIBBS, ALBERTO FOIS, and FREDERIC A. GIBBS, New England J. Med. 253:1102 (Dec. 22) 1955.

In 51 cases of retrolental fibroplasia electroencephalographic recordings were obtained in the waking and sleeping states. Although only 27% of patients had some form of clinical epilepsy, seizure activity was present in 88% of the entire group (in 100% of those with seizures and in 70% of those without seizures). The clinical history of seizures and the occurrence of mental retardation suggested brain disorder in some cases, but the present study indicates that brain disorder may occur in cases of retrolental fibroplasia.

The frequency of seizure activity among younger and older children differed; 50% of those under and 97% of those over 3 years of age had seizure activity. The commonest electroencephalographic abnormality was a focus of spike-seizure activity in one or both occipital areas. This occurred in 35% of children under and 74% of those over 3 years of age. Follow-up studies on children with occipital-lobe foci have shown that this type of focus tends to disappear with increasing age or to migrate into the midtemporal region.

The following circumstances are considered possible causes of the seizure activity in retrolental fibroplasia: trans-synaptic degenerative changes in the brain secondary to blindness in early infancy (structural evidence of such changes has been reported by Von Gudden); oxygen poisoning of the immature brain resulting from excess oxygen in the respired air, and premature photic stimulation.

WHEELOCK, Washington, D. C.

ENCEPHALITIS POSTVACCINALIS. Prof. Dr. J. D. VERLINDE, Nederl. tijdschr. geneesk. 99:1020-1025 (April 2) 1955.

In this investigation 53 monkeys were infected cutaneously with vaccinia virus and intramuscularly with a strain from the Columbia SK group. This strain had been isolated from

the feces and the throat secretions of a child suffering from postvaccinal encephalitis. Only one of these monkeys developed the characteristic histological picture of postvaccinal encephalitis. The combined action of this virus, which is neurotropic for experimental animals and the vaccinia virus as a possible etiological factor in this disease, is critically discussed.

VAN CREVELD, Amsterdam

INVESTIGATION ON THE CONTENT OF DIFFERENT AMINO ACIDS OF THE CEREBROSPINAL FLUID. T. H. J. HUISMAN, Nederl. tijdschr. geneesk. 99:3357 (July) 1955.

By way of column chromatography the amino-acid content and the distribution of different amino acids were determined in the cerebrospinal fluid after deproteinization by means of ultrafiltration before and after hydrolysis.

In both cases the amino-acid content was shown to be very low, with the exception of glutamic acid and glutamine of which the concentration is considerably higher.

VAN CREVELD, Amsterdam

Psychology and Psychiatry

INTEGRATING SPEECH THERAPY WITH LANGUAGE ARTS. EDDIE LEE SUTTON, J. Speech & Hearing Disorders 20:376-379 (Dec.) 1955.

Discussion of a curricular integration of speech therapy with language arts in the elementary school. Speech therapy can be reinforced by integrating it with at least one other complimentary phase of learning. A suggested graded list of objectives beginning with kindergarten through the fifth grade is given.

PALMER, Wichita, Kan.

A METHOD OF THERAPY FOR PARALYTIC CONDITIONS OF THE MECHANISMS OF PHONATION RESPIRATION AND GLUTINATION. EMIL FROESCHELS, SHULAMITH KASTEIN AND DESO A. WEISS, J. Speech & Hearing Disorders 20:365-370 (Dec.) 1955.

Pushing exercises in which a patient is instructed to raise his fists to his chest, push his arms down in one quick, elastic sweep, with fingers closed, at the same time the patient says "AH," have been used in patients with abductor and adductor paralysis by Weiss and in patients with diseases of the central nervous system involving phonation, breathing, and swallowing by Kastein. The authors feel this technique useful in bulbar poliomyelitis, progressive bulbar paralysis, pseudobulbar paralysis, Parkinson's disease and muscular dystrophy.

PALMER, Wichita, Kan.

A STUDY OF THE RELATIONSHIP BETWEEN ARTICULATORY ABILITY AND LANGUAGE ABILITY. NORMA SCHNEIDERMAN, J. Speech & Hearing Disorders 20:359-363 (Dec.) 1955.

Seventy children in first grade classes, ranging in age from 6 years to 7 years 1 mo., 41 boys and 20 girls thought to have no organic etiology or mental retardation, where studied on three tests of language ability: Van Alstyne Picture Vocabulary Test, Gates Reading Vocabulary list, and a rating by classroom teachers, on the ability to express themselves in language. The intercorrelations between the three tests of language ability show they formed a valid measure of general language skill. There appears to be a relationship between articulatory ability and language ability in children.

PALMER, Wichita, Kan.

Diseases of Ductless Glands; Endocrinology

A CASE OF SPONTANEOUS HYPOGLYCEMIA. J. ENGELHARDT, K. KRAAYENBRINK, and V. H. DE VILLENEUVE, Maandschr. kindergeneesk. 23:85 (March) 1955.

Description of a 10-month-old boy with convulsions since the age of 4 months and abnormal low blood-sugar values. There was some retardation of bodily and mental development. No diabetes or epilepsy in the family.

On accunt of the considerably raised tolerance for intravenously administered glucose, and of the increased insulin content of the blood, the presence of an insulinoma was suspected.

Before performing laparotomy the child was treated with cortisone, ACTH, and growth-hormone on account of observations by McQuarrie and others, but without any result. Subsequent laparotomy did not reveal the presence of an insulinoma. Subtotal resection of the

pancreas was then performed; pathologic-anatomical examination revealed multiple, microscopically large, beta-cell adenomata (method of coloring of Gomori).

The child recovered and did not have any convulsion to the moment of publication (i.e., six months later).

VAN CREVELD, Amsterdam

ADRENOCORTICAL CARCINOMA, ABSENCE OF SYMPTOMS IN A PATIENT, 4 YEARS AFTER REMOVAL OF THE TUMOR. PH. ARONS and J. I. DE BRUIJNE, Maandschr. kindergeneesk. 23: 111 (April) 1955.

Description of a nearly 2-year-old girl with an adrenogenital syndrome as a result of adrenocortical carcinoma. Four years after the extirpation of the tumor the little patient is still in good health. Since the operation the excretion of 17-ketosteroids has consistently remained low. Methods to be followed before, during, and after the operation are discussed.

VAN CREVELD, Amsterdam

INCREASE OF ALDOSTERONE EXCRETION IN CONGENITAL ADRENOGENITAL SYNDROME: A CONTRIBUTION TO THE PATHOGENESIS OF THE SYNDROME A. PRADER, A. SPAHR, and R. NEHER, Schweiz. med. Wchnschr. 85:1085-1088 (Nov. 5) 1955.

The normal urinary aldosterone excretion, measured with the method of Neher-Wettstein, is 0.3 to 3.5 gamma in 24 hours and for adults 0.5 to 5.0 gamma in 24 hours. Three infants with the congenital adrenogenital salt-losing syndrome excreted a normal or slightly increased amount of aldosterone. One of these died the day after the determination. A child with a healed salt-losing syndrome excreted 59 gamma aldosterone in 24 hours. The results are cited as another proof that the adrenogenital salt-losing syndrome is caused by an unidentified Na-excreting adrenocortical factor. Increased Na intake and cortisone lower the aldosterone excretion. For further data the paper should be consulted.

AMBERG, Rochester, Minn.

EARLY DIAGNOSIS OF OLIGOPHRENIA PHENYLPYRUVICA. W. FRISCHKNECHT, Schweiz. med. Wchnschr. 85:969-970, 1955.

In spite of congenital oligophrenia phenylpyruvica an infant may develop to an age of 6-7 months apparently normally. Later the mental and somatic retardation become evident. The diagnosis can be made before this time by testing the urine with a 5% ferric chloride solution which in the presence of phenylpyruvic acid gives an olive-green color. A peculiar mousy odor of the skin of light blond pasty infants inclined to dermatitis may arouse suspicion. Two girls with the disease are reported, one seen at an age of 13 months, the other at an age of 2½ years. The early diagnosis is important so that a diet poor in phenylalanine can be instituted in infancy. Aside from an increase of phenylalanine Valin, Alanin, Seryl-Glycyl-Glycin were increased in the urine in one case, in the other glykokoll and asparagin were found in the urine in addition.

DIABETES INSIPIDUS MASKED BY LESIONS OF THE ANTERIOR PITUITARY LOBE. E. HERRMANN, Schweiz. med. Wchnschr. 85:1041, 1955.

A boy 11 years of age acquired a diabetes insipidus which in the further course disappeared with the appearance of an insufficiency of the anterior pituitary. With its development growth and body weight were arrested in addition to other manifestations of cessation of anterior pituitary function. Another boy, 13 years of age, also acquired a diabetes insipidus which did not reach any severe degree, evidently because at the same time a lesion interfering with the function of the anterior pituitary exercised its influence. Here a tumor in the region of the third ventricle was held responsible. In a third case, that of a 32-year-old man, diabetes insipidus fully developed slowly but became modified after 5 years by an insufficiency of the anterior pituitary, for unknown reasons. In the first two cases administration of ACTH or cortisone led to a recurrence of the diabetes insipidus. For a more detailed discussion the paper should be consulted.

A CLINICAL-EXPERIMENTAL STUDY OF THE EFFECTS OF DESOXYCORTICOSTERONE ACETATE IN THE METABOLISM OF CHILDREN. M. MALASPINA and E. ARDITI, Minerva Pediat. 7:1433 (Nov. 10) 1955.

Three healthy children and two children with chronic dyspepsia and three with celiac disease were put on a fixed diet containing 40 gm. of fat. Analyses of the fecal lipids were

made before and after the children had been receiving for 12 days daily doses of 2 to 3 mg. desoxycorticosterone. There were no appreciable changes in the amount or distribution of the fecal fats of the normal children. In the cases of the other children, there was a 50% drop in the amount of fecal fat following the medication.

HIGGINS, Boston

SECONDARY HEPATIC GLYCOGENOSIS: A PREVIOUSLY NOT RECORDED FINDING IN THE COURSE OF INFECTIOUS HEPATITIS, AS SHOWN BY NEEDLE-PUNCTURE BIOPSIES. R. BULGARELLI and F. DE MATTEIS, Minerva Pediat. 7:1413 (Nov. 10) 1955.

Biopsies by needle puncture were made of the livers of 32 children (1 month to 9 years old) with infectious hepatitis. Glycogenosis was found in seven cases; in these cases the liver was noted to be of a firmer consistency by palpation. Five of these seven children recovered in short order, and subsequent biopsies on several revealed that the glycogenosis was no longer present. The other two children had a more chronic type of hepatitis with sclerosis as well as glycogenosis. Attention is called to the fact that the livers in some cases of Gierke's disease also have sclerosis as well as glycogenosis.

HIGGINS, Boston

COMPARATIVE EXAMINATION OF 2 GROUPS OF CHILDREN, RESPECTIVELY WITH AND WITHOUT GOITRE CONCERNING GROWTH AND DEVELOPMENT. J. F. DE WIJN, Maandschr. kindergeneesk. 23:132 (April) 1955.

Neither a nutrition inquiry nor the nutritional state judged by height and weight shows important differences with respect to the nutrition of children with and without goiter. However, bodily development, onset of puberty, systolic blood pressure, alkaline phosphatase, and inorganic phosphate show a retardation in children with goiter in comparison with goiter-free children. However, the differences are small.

VAN CREVELD, Amsterdam

A NEW ANTIDIABETIC PRINCIPLE. H. FRANKE UND J. FUCHS; A NEW BLOOD SUGAR LOWERING SUBSTANCE. J. D. ACHELIS and K. HARDEBECK; A POTENT PERORAL ANTIDIABETIC DRUG. FERDINAND BERTRAM, ELINOR BENDFELDT, und HELLMUT OTTO, Deutsche med. Wchnschr. 80:1449-1460, 1955.

These three papers deal with the effect of BZ55, (C. F. Boehringer and Söhne, Mannheim-Waldhof.) N_1-sulfanilyl-N_2-n-butylcarbamid, a new sulfonamide, on the blood-sugar level. Besides the advantage of an antibacterial agent of a relatively high sulfonamide content of the blood on low dosage given by mouth it causes a definite lowering of the blood sugar. It has been used successfully in cases of diabetes mellitus without insulin or reducing the insulin requirement. In cases of juvenile diabetes the prospects for beneficial results are not very good.

The assumption of an effect on the alpha cells of the pancreas (the glycogen producers) has been supported by animal experiments. The last paper requests that the general use of the drug should be deferred until more extensive data are available.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

PROGRESSIVE MUSCULAR DYSTROPHY AND THE EFFECT OF HORMONE TREATMENT. J. A. TAZELAAR, Nederl. tijdschr. geneesk. 99:2496 (Aug. 20) 1955.

After reviewing creatine and creatinine metabolism under normal and pathological conditions, the author presents some graphs illustrating the results obtained by prolonged treatment of progressive muscular dystrophy in 20 male patients with testosterone derivatives. The results of vitamin B_{12} and DFP treatment are also reported.

The results of testosterone derivatives have proved to be favorable; DFP and vitamin B_{12} do not effect any improvement.

The author concludes that the effect of hormone therapy can only be judged by physical examination and information supplied by the patient. Creatine and creatinine secretion are not reliable criteria.

VAN CREVELD, Amsterdam

ANHIDROSIS POLYDYSPLASTICA. G. A. VERSTEGE, Nederl. tijdschr geneesk. 99:2785 (Sept. 17) 1955.

Report on a boy aged 5 years and a man (professional diver) aged 34 years, with the typical syndrome of polydysplastic anhidrosis (Siemens).

The symptomatology of the syndrome (anhidrosis, hypotrichosis, hypodontia, atrophic rhinitis, characteristic form of the face) and the heredity are reviewed. The syndrome is clearly defined with respect to other types of ectodermal dysplasia, and a case of *onychodystrophia cum hypodontia* is reported. "Congenital ectodermal defect" and "hereditary ectodermal dysplasia" are synonyms which have given rise to much confusion. There are many congenital defects of the ectoderm; several are hereditary, some are dominant and others are recessive, sex-linked or not. It is therefore advisable to give such a well-defined syndrome a name of its own. The term "anhidrosis" is justified, because clinically the inability to sweat is conspicuous. Another striking characteristic of the syndrome is polydysplasia, which is shown in a great variety of symptoms. Therefore "anhidrosis polydysplastica" is an obvious name.

Other types of so-called ectodermal dysplasia are merely combinations of anomalies of hair and nails, which may be combined with dental dysplasia; they do not really represent generalized dysplasia. For the pediatrician it is important to know that these children are very often admitted to hospital on warm summer days with the diagnosis *"febris e causa ignota."*

VAN CREVELD, Amsterdam

CONGENITAL AND INFANTILE MYASTHENIA. A. BIEMOND and L. VAN TROTSENBURG, Maandschr. kindergeneesk. 23:155 (May) 1955.

The authors describe three cases of infantile congenital myasthenia, which had a subacute commencement and developed in an extreme severe clinical picture. The disturbances in breathing and swallowing are predominating, but a general muscle slackness is evident. In one of the cases infection of the upper airways had a clearly provocative influence. A subcutaneous injection of ¼ mg. Prostigmin is of great diagnostic importance.

In two cases a pathological examination was made. No abnormalities were found in the central nervous system.

Myasthenia which always has been considered as a typical disease in adults between 15 and 50 years, has been described in the last few years in children and infants. It appears from the literature that myasthenia in young children and infants often has an acute occurrence in the form of attacks, a predominance of disturbances in breathing and swallowing and frequently a familiar incidence.

VAN CREVELD, Amsterdam

OSTEOCHONDROMATOSIS DEFORMANS TIBIAE IN CHILDREN. J. E. ENKLAAR, Amsterdam (the Netherlands). Maandschr. kindergeneesk. 23:234 (July) 1955.

A 3-year-old girl with bowlegs due to osteochondrosis deformans tibiae is described. A brief review is given of the principal literature. Blount (1937) was the first to describe this disease in the growing child. This rather unknown disease probably is not rarely the causative factor for the occurrence of bowlegs which, failing radiologic examination, till now are regarded as being of physiological or rachitic origin. The etiology is still unknown, but the possibility of spontaneous regression in an early stage is generally accepted.

The typical histological symptoms are described as persistent cartilage islands of the proximal epi- and metaphysis of the tibia with hypertrophic cells, acellular fibrous cartilage, and excessive capillar growth. The diagnosis in the early stage is made by x-ray pictures.

The usual terminology in the English literature, viz., tibia vara or nonrachitic bowlegs, is considered unpractical, partly because in some cases of knock-knees a similar x-ray picture was found in the lateral half of the knee. Routine x-ray examination of knock-knees and bowlegs in two 6-year-old children is essential for the timely discovery of those due to osteochondrosis.

VAN CREVELD, Amsterdam

THE SPONDYLITIS OF JUVENILE RHEUMATOID ARTHRITIS, ROBERT E. BARKIN, SYDNEY STILLMAN, and THEODORE A. POTTER, New England J. Med. 253:1107 (Dec. 22) 1955.

In a series of 71 children with juvenile rheumatoid arthritis, 57 (80%) gave clinical or x-ray evidence of spinal involvement.

The areas most commonly involved were the neck and lower back.

Calcification of the paravertebral ligaments was unusual, being noted in only two cases in this series even with long follow-up periods.

In this group of children, rheumatoid spondylitis was always accompanied by peripheral joint involvement and never existed as an entity.

WHEELOCK, Washington, D. C.

Pseudohypertrophic Muscular Dystrophy in 3 Brothers. Lucrecia Hernandez R., Rev. Hosp. Nino 57:387-404 (March) 1954.

The author reports three cases of pseudohypertrophic muscular dystrophy in brothers, demonstrating the familial character of this disease. In one case there appeared to be endocrine disturbance. The treatment with vitamin E and other vitamins was given without any satisfactory results.

There are photographs and a detailed chart of the family tree. There is considerable discussion of the pathology and differential diagnosis.

Keith, Rochester, Minn.

Epiphyseal Stimulation in the Lower Extremities. Warren G. Kramer, California Med. 83:424 (Dec.) 1955.

Epiphyseal stimulation to correct disparity in the length of lower extremities was done in 12 children. The total number of procedures was 15. In 11 of the 15 instances the operation was beneficial. Ivory pegs were used in some cases, brass screws in others, and multiple drill holes in still others. There seemed to be no difference between them in the amount of stimulation brought about.

Stimulation persisted for from 6 to 10 months after operation.

Complications that may occur are varus or valgus deformities, delay in growth, complete fusion, or infection. To prevent varus or valgus deformity, both medial and lateral sides may be stimulated simultaneously. Great care must be taken to place the screws no closer than ¼ in. to the epiphyseal plate to avert trauma which may delay rather than stimulate growth. Late infection may be obviated by the use of absorbable materials.

The increase brought about by stimulation procedures is probably attributable to hyperemia following subperiosteal stripping.

Stenosis of the Fibrous Tendon Sheath of the Flexor Longus of the Thumb in Children. J. Muller and F. Willemijn, Maandschr. kindergeneesk. 23:29 (Jan.) 1955.

Five cases of children with stenosis of the fibrous tendon sheath of the flexor longus of the thumb are described. The extension of the thumb is difficult and it gives rise to a flexion contracture. The origin of the stenosis is unknown. Probably it is of congenital origin, because it is seen in very young infants, and it occurs lateral and in twins.

The most important sign is not "the snapping thumb" as in adults, but the apparent flexion-contracture in the interphalangeal joint. An operation is necessary because the conservative method gives no results. The prognosis is good, when the stenosis has completely disappeared. In two cases the apparent flexion contracture could not be passively relieved. In two other cases this was possible, and in one case the contracture occurred intermittently. In all cases a surgical operation was performed, followed by complete recovery.

van Creveld, Amsterdam

Rickets. J. H. P. Jonxis, Maandschr. kindergeneesk. 23:253 (July) 1955.

A brief review of the history of rickets is given. The exact mode of action of vitamin D in the body is still unknown. The relation between vitamin D, phosphate metabolism, and aminoaciduria is investigated. It is found that the excretion of amino acids in the urine is increased in rickets, especially in resistant rickets. Only a few number of amino acids are concerned and the plasma level is not raised.

In early rickets an increased excretion of amino acids is the first symptom. Some cases of cured rickets still show an excretion of amino acids higher than normal, which suggests a familiar disposition in rickets. There is no reason to accept that the amino acids are excreted as phosphate esters, since phosphate loading did not raise the excretion of amino acids in the urine.

Further investigations showed that phosphate loading, especially in moderate rickets, reduced the calcium level in the blood, and tetania followed. In the northern part of the Netherlands where cow milk is abundantly given to children in springtime more cases of tetania are observed.

Only the character of the kidney dysfunction in vitamin-D deficiency can be understood until now. Vitamin D is necessary for the normal function of some enzyme systems which regulate the normal reabsorption of phosphates and amino acids in the tubules of the kidney.

It is supposed that in rickets and some inborn errors of metabolism, such as resistant rickets and the Debré-de Toni-Fanconi syndrome, there exists an abnormal function of the enzyme system.

VAN CREVELD, Amsterdam.

TREATMENT OF SPASTIC CHILDREN. K. A. MELIN and E. ROBERTSON, Deutsche. med. Wchnschr. 80:1599-1603, 1955.

Children with motor disturbances, spasms, athetosis, ataxia, motor paralysis, and myasthenia are included. It is emphasized that a diagnosis within the first two years of life is necessary to obtain good therapeutic results by the methods outlined. Cooperation of various branches of medicine is required.

Diseases of Eye

TREATMENT OF RETROLENTAL FIBROPLASIA. W. A. MANSCHOT, Nederl. tijdschr. geneesk. 99:3838 (Dec. 17) 1955.

Since the role of high oxygen concentrations in the development of retrolental fibroplasia has been recognized, one is inclined to omit the oxygen after the appearance of symptoms of retrolental fibroplasia. Nevertheless experiences have been described of improvement of the disease when oxygen was given again.

One of the first symptoms of retrolental fibroplasia is edema of the retina. Manschot describes a premature baby of 1000 gm. who was nursed during one month in an oxygen atmosphere of about 65%. Retinal edema appeared when no oxygen was given after that month; however, it disappeared when oxygen was given again. During the next two months, the oxygen was omitted four times and every time edema of the retina appeared again; only when the child reached a weight of 3000 gm. was it completely cured.

VAN CREVELD, Amsterdam.

RETROLENTAL FIBROPLASIA AND INTERSTITIAL PNEUMONIA. W. A. MANSCHOT and M. STRAUB, Nederl. tijschr. geneesk. 99:92 (Jan. 8) 1955.

One hundred fourteen eyes of 59 premature infants who had not undergone an ophthalmological examination were anatomically examined. The first stages of retrolental fibroplasia, characterized by retinal edema and proliferation of the capillary-forming mesenchymal cells in the nerve tissue, were found in the eyes of three children.

Hemorrhagia of the retina and glia growth are not observed in all cases. The authors believe that these last mentioned symptoms are no distinguishing marks.

It is determined that in hypoxic retinae of premature infants the proliferation of the capillaries is stimulated. The lungs of these three infants showed a subchronic interstitial pneumonia corresponding with an advanced stage of interstitial pneumonia of premature infants.

It appears from the literature that in some clinics more than 50% of all premature babies weighing less than 1500 gm. at birth suffer from interstitial plasmacellular pneumonia. This is the group of premature infants in which most cases of retrolental fibroplasia occur. The clinical and anatomical pictures of interstitial pneumonia prove that these patients are severely hypoxic. Retrolental fibroplasia is ultimately due to retinal hypoxia.

It is supposed that the high oxygen concentrations in the incubators stimulate the growth of the pneumocystes, which are the causative agents of the interstitial pneumonia and chiefly are found in the bronchioli and alveoli. Also the use of antibiotics, especially penicillin should stimulate the growth of the pneumocystes. The three patients were treated with penicillin. It is highly probable that in many cases of retrolental fibroplasia this retinal hypoxia is caused by interstitial plasma cellular pneumonia. This could explain the epidemical incidence of retrolental fibroplasia.

VAN CREVELD, Amsterdam.

Teeth and Dentistry

RECURRENT INTUSSUSCEPTION ASSOCIATED WITH HYPERTROPHY OF PEYER'S PATCHES. ERNEST L. SARASON, JOHN T. PRIOR, and RALPH L. PROWDA, New England J. Med. 253:905 (Nov. 24) 1955.

The general problem of recurrent intussusception in infants and children is reviewed. The clinical and pathological findings in a patient who underwent five operative reductions of recur-

rent ilecolic intussusceptions, after which ileocecal resection was performed with success, are reported. The cause of the recurrent intussusception was a tumor mass in the terminal ileum that on microscopical examination proved to be characteristic of giant-follicle hypertrophy of Peyer's patches in the wall of the ileum.

The pathological features of this entity and its relation to the normal lymphatic apparatus of an infant, as well as to other diseases of the lymphoid system, are discussed.

On the basis of this, together with a survey of the literature, ileocecal resection appears to be warranted if an ilecolic intussusception recurs more than once even though no tumor can be palpated within the terminal ileum.

WHEELOCK, Washington, D. C.

EXTENSIVE BURNS IN CHILDREN: TREATMENT OF THE EARLY PHASE. EDWARD H. SENZ, California Med. 83:362 (Nov.) 1955.

The water, electrolyte, and colloid losses and shifts which occur after a severe burning are complex and variable from patient to patient. No available clinical method allows for accurate prediction of the volume and composition of the fluid losses. The method here described assumes that parenteral therapy which produces a normal urinary output and maintains the child free of signs and symptoms of shock is good therapy and at least approximates his needs. On the whole this assumption has been verified by clinical experience.

Once again it is necessary to stress the importance of treatment that anticipates needs rather than treatment which comes after unmet needs are obvious.

Methods used to assess and treat burned adults need modification before application to infants and children.

FULL-TERM BIRTH OF THE FRISIAN CONJOINED TWINS. J. P. S. WIJTHOFF, Nederl. tijdschr. geneesk. 99:3604 (Nov. 26) 1955.

Report on the normal birth of a pair of twins conjoined at the abdomen, both showing cranial presentation.

The delivery was done at home in primitive circumstances with great technical difficulties. A spontaneous movement on a longitudinal axis was initially seen; the children were subsequently forced by a few manipulations to execute a rotating movement in a sagittal plane on a horizontal axis traversing the symphysis and the superior rami of the pubic bones. As a result the second child was born in breech presentation so that only one child at a time passed the pelvic outlet.

The surgical separation of the twin was accomplished with good result by a team consisting of one pediatrician, four surgeons, and two anesthesists. An extensive report will be given in the *Archivum chirurgicum neerlandicum*.

VAN CREVELD, Amsterdam.

News and Comment

ANNOUNCEMENTS

Congress of the International Union Against Cancer.—The Seventh International Cancer Congress will be held in London, England, July 6-12, 1958, under the Presidency of Sir Stanford Cade. Congress headquarters will be The Royal Festival Hall.

There will be two main sessions of the Congress:

A. Experimental

B. Clinical and Cancer Control

Special emphasis will be placed on hormones and cancer, chemotherapy, carcinogenesis, and cancer of the lung.

Proffered papers will only be considered if submitted with an accompanying abstract (not over 200 words) before October, 1957, and if dealing with new and unpublished work.

The registration fee for the Congress will be £ 10 (ten pounds) or $30 (thirty dollars) and the latest date for registration without late fee will be Jan. 1, 1958.

Registration forms and a preliminary program will be available early in 1957 on application to The Secretary General, Seventh International Cancer Congress, 45 Lincoln's Inn Fields, London, W. C. 2, England.

GENERAL NEWS

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by The American Board of Pediatrics, Inc., in New York on Oct. 12, 13, and 14, 1956.

Abbuhl, John W., Albany, N. Y.
Almon, David Thixton, Pomona, Calif.
Arnold, John Hampton, Boston.
Arnold, Mary B., Boston.
Ashe, Barbara S., New York.

Baker, David, Broomall, Pa.
Beasley, Jean T., Westport, Conn.
Beirne, Donald Peter, East Orange, N. J.
Bunce, John D., Falls Church, Va.

Chambers, Van Vleck, Rochester, N. Y.
Charles, Walter A., Syracuse, N. Y.
Clemmens, Raymond L., Baltimore.
Coddington, Robert Dean, Red Bank, N. J.
Cohen, George J., Silver Spring, Md.
Cohen, Solomon Jay, Westfield, N. J.
Colucci, John A., Jr., Massapequa, L. I., N. Y.
Conley, John Ruppert, Kensington, Md.
Curtis, Robert Anderson, Anaheim, Calif.

Di Leo, Vincent Louis, New Orleans.

Farley, William, Raleigh, N. C.
Frost, Loraine Hulburd, Iowa City.

George, Gerald Y., Bellaire, Texas.
George, John W., New York.
Giffin, Robert Burns, Jr., New York.
Goalwin, Alta Tresa, New York.
Gonzalez, Jose Luis, Portsmouth, N. H.
Gould, Samuel Halpert, Hopewell, Va.

Harris, Seymour Jay, Oakland, Calif.
Hart, William Edmund, Hartford, Conn.
Herman, Robert Mitchell, Palo Alto, Calif.
Hoffman, Martin A., Richmond, Va.
Humphreys, Elizabeth Drake, Bennington, Vt.

Joy, Robert Chamberlain, Danbury, Conn.

Kizer, Betty Jane, Glen Ellyn, Ill.
Latham, Elizabeth Boykin, Aiken, S. C.
Lavendel, Evelyn, Jackson Heights, N. Y.
Levitsky, David A., Wilmington, Del.
Limosani, Michael Anthony, Chicago.
Lockhart, Jean Douglas, Alexandria, Va.
Lustick, Bernard R., Watertown, N. Y.

McDonald, John J., Whittier, Calif.
McGrady, Kathleen Reilly, Hialeah, Fla.
McIntire, Matilda Stewart, Omaha.
McNeil, James L., El Paso, Texas.

Mann, Martha E., Baltimore.
Marans, Allen Elias, Silver Spring, Md.
Marks, Dennis Nicholas, Sacramento, Calif.
Martel, Norman G., Los Angeles.
Menzer, Alexander, Hartford, Conn.
Miller, Bennett, York, Pa.
Mofenson, Howard C., Mineola, N. Y.

Munoz, Aurea I., Hato Rey, Puerto Rico.
Myers, Richard Lyon, Rochester, Minn.
Neuenschwander, Robert S., Covina, Calif.
Oberman, J. William, Washington, D. C.
Pendleton, Murray Ethan, Brookline, Mass.
Penn, Edward A., Fall River, Mass.
Pennington, Katherine, Wichita, Kan.
Pinkel, Donald Paul, Buffalo, N. Y.
Piovanetti, Simon, Santurce, Puerto Rico.
Pryles, Charles Victor, Boston.
Pugh, Richard G., Kansas City, Mo.
Rachelson, Morton H., Verona, N. J.
Robinson, Thomas, Muncie, Ind.
Schmidt, Evelyn D., N. Plainfield, N. J.
Schwartz, Bertram Saul, Hicksville, N. Y.
Sohn, William J., Hatboro, Pa.
Stankewick, Walter Richard, Garden City, N. Y.
Stekler, Burton Lester, Glen Rock, N. J.
Strassman, Selig Simon, Shaker Heights, Ohio.
Summer, George Kendrick, Chapel Hill, N. C.
Taft, Lawrence Tedford, New York.
Tanis, Arnold Lawrence, Key West, Fla.
Toomim, Leonard A., Beaumont, Texas.
Tufts, Emily, Pinehurst, N. C.
Turano, Andrew F., Middletown, Conn.
Wax, Florence S., New York.
Wineland, Robert Kenneth, Alexandria, Va.
Winston, John S., Forest Hills, N. Y.
Wittig, Heinz J., New York.
Wood, Judith Lee, Glenview, Ill.

Special Foreign Certificates:

Espinosa, Purification M., Cebu City, Philippines.
Slungaard, Rolv Kjelberg, La Crosse, Wis.

The following Special Foreign Candidate could not be listed previously as we had not received the address in India. It is as follows:

Lall, Seeta, Bombay, India.

PERSONAL

Appointment of Dr. Robert B. Livingston.—Dr. Robert B. Livingston has been appointed Scientific Director of the combined basic research programs of the National Institute of Mental Health and the National Institute of Neurological Diseases and Blindness in Bethesda, Md. The announcement was made by Dr. James A. Shannon, Director of the National Institutes of Health, who said that Dr. Livingston will assume his new position on November 15.

Dr. Livingston succeeds Dr. Seymour S. Kety, who has asked that he be relieved from the position of Scientific Director in order to devote full time to his own laboratory investigations in the field of cerebral blood flow.

Dr. Livingston comes to the Public Health Service from the University of California Medical School at Los Angeles, where he has been associate professor of physiology and anatomy.

ANNOUNCEMENTS

Symposium on Iron in Clinical Medicine.—An "International Symposium on Iron in Clinical Medicine" is planned for Jan. 28 and 29, 1957, at the University of California Medical Center in San Francisco.

Several authorities in the role of iron therapy in clinical medicine will discuss such topics as "Iron Metabolism—Basic Principles"; "Iron in Pediatrics"; "Iron Deficiency Anemia," and "Abnormal Iron Metabolism."

The two-day symposium is presented by the University of California Medical Center and Medical Extension together with the Children's Hospital of San Francisco.

Program chairmen will be Dr. Ralph O. Wallerstein, clinical, instructor in medicine at the University, and Dr. Stacy R. Mettier, professor of medicine.

Members of the staff will include experts from England, Germany, and Sweden and from several American universities and medical centers.

Ample time will be given to a review of current research concepts, although the orientation of the symposium is primarily clinical. Specific problems in the various specialties will be dealt with.

Books

BOOK REVIEWS

Case Studies in Childhood Emotional Disabilities. Volume II. Edited by George E. Gardner. Price, $5. Pp. 368. American Orthopsychiatric Association, 1790 Broadway, New York 19, 1956.

This book comprises a collection of case studies presented and discussed at "Workshops" of the American Orthopsychiatric Association. It is basically designed to serve as teaching material for the three disciplines involved in the care of emotionally disturbed children: child psychiatry, clinical psychology, and psychiatric social work.

Of the total of 15 papers 4 deal with the age period from 5 to 6 years, a period of development which—as known to any pediatrician—is filled with emotional problems as the child, on one hand, struggles with his desire to free himself emotionally from the tie to his parents and, on the other hand, has to live with his parents who may wish to hold on to the "baby" and at the same time may want to rid him of his babyishness. Two of these cases are concerned with encopresis. Three papers are devoted to adolescent problems (mostly delinquent behavior). Others are concerned with school problems, adjustment of the blind child, management of a destructive hyperactive child, and two papers deal with near-psychotic children.

As teaching material for teams involved in such treatment of emotionally disturbed children this book contains excellently selected material, well presented in concise and clear form and instructively discussed and interpreted. The pediatrician, on the other hand, may find the presentations too lengthy and too detailed with psychoanalytic interpretations unless his interest is directed in this line and he has had some basic training in this theory and is inclined to accept it.

La Salud del Hijo. By Juan P. Garrahan. Price, not given. Pp. 603. Libreria "El Ateneo" Editorial, Florida 340, Buenos Aires, Argentina, 1955.

This book is written by Dr. Juan P. Garrahan, Professor of Pediatrics at the University of Buenos Aires, primarily for the use of General Practitioners, nurses, and nursery personnel, but it would be of great benefit to any young couple interested in the proper handling of their children. It is written in everyday language and covers very adequately the care of infants and children. If this book ever became the Spanish counterpart of Dr. Spock's book, it would certainly mean an improvement in the pediatric care of Spanish-American children. It is up to date and in agreement with the most modern pediatric concepts relating to feeding, medical and surgical care, and social development. It has an adequate bibliography but lacks a more workable index.

Die Genuine Vitamin-D Resistente Rachitis. By Dr. Walter Swoboda. Price, $2.50. Pp. 80, with 12 illustrations. Wilhelm Maudrich, Vienna, Austria, 1955.

To this reviewer's knowledge this is the first attempt to present in definitive monographic form the subject of vitamin D-resistant rickets. The clinical and roentgenologic aspects are presented in detail as are the problems of medical and orthopedic management. The literature on the subject is well and completely covered. The authors rather extended experience with 11 cases of D-resistant rickets is given in some detail. Original comparative data on the renal clearance of phosphorous in normal persons and in patients with D-deficient and D-resistant rickets before and after the administration of vitamin D are presented. Data are presented indicating abnormal quantitative distributions of ATP and phosphocreatine in the erythrocytes of patients with the disease. The nature of the enzymatic deficit is speculated about. This monograph will be of value to those who must care for children with the disease and of particular interest to those interested in the basic problems of calcium and phosphorous metabolism.

Premature Infants. Ed. 2. By Ethel C. Dunham. Price, $8. Pp. 458, with 41 illustrations. Paul B. Hoeber, Inc., Med. Book Dept. of Harper & Brothers 49 East 33rd Street New York 16, 1955.

The new second edition of Dr. Dunham's book is to the first edition as a term baby is to a premature. It is grown-up and full-sized. From a paper-bound pamphlet, this fine text on all phases of the premature baby has grown into a hard-covered, well-printed reference book of some 457 pages.

The general organization of material in the book is similar to the previous edition, being divided into three sections: general considerations, clinical considerations, and public health aspects. However, each section has been enlarged, brought up to date, and made more readable.

In the first section recent data have been included on mortality, growth and development, and the prognosis for premature infants. Of particular interest are the data pertaining to the Hess long-term follow-up on a group of small babies, and the recent interest in the emotional reaction of the premature. The effects of long hospitalization are mentioned.

The clinical considerations are particularly complete and up to date with pertinent discussions on retrolental fibroplasia, hyaline membrane disease, polyethylene indwelling, tube technique, humidity control, as well as the many variations of congenital malformations and metobolic diseases. The objectivity in the evaluation of these conditions is refreshing and stimulating.

The public health aspects are well covered and are a help to anyone concerned with running a premature center or station where comparison with other institutions is desired.

All in all, the book is well illustrated, the references to the literature are current and well selected, and the format conducive to frequent study.

This book is a must for all concerned with premature care.

Special Education for the Exceptional. Three Volumes. By Merle E. Frampton and Elena D. Gall. Price, $5.50. Pp. Vol. I, 453; Vol. II, 677; Vol. III, 700. Porter Sargent, 11 Beacon Street Boston 8, 1955.

This work is a source of information of exceptional thoroughness serving not only the educator, as the title may indicate, but everyone concerned with the care of children—thus also exceptional children.

The physician attending to children will directly or indirectly be constantly dealing with handicapped children whose total percentage of the school population is estimated at 12.7. In his contact with parents, teachers, social workers, rehabilitation personnel, medical colleagues, and counsellors, he will himself be able to utilize these three volumes for reference and refer others to chapters pertaining to the special problem.

The text of each chapter is followed by a long list of references which facilitates further study of a specific problem without long searching for pertinent literature. At the end of the book general references by the hundreds are arranged according to disciplines. A comprehensive list of agencies devoted to the service of special handicaps is a valuable source of further information as well as of actual help for the handicapped child.

The term "exceptional" is broadly interpreted: apart from the exceptionally gifted as well as the handicapped child it includes such handicaps as problems of the aged, the chronically ill, the narcotic, and the alcoholic which affect the adult rather than the child.

The first volume defines the handicaps and educational needs common to all and specific for each. In addition, it contains statistical data and general discussion of the problems, such as mental health, educational and administrative problems, teachers' training, and parent education. The special value of this volume for the pediatrician lies in the definition and clarification of the problems, the statistical data, and especially the references of literature material as well as agency resources.

The second volume discusses specific handicaps and their special problems. It includes blindness and deafness, both partial and total, each covered in separate comprehensive chapters; speech defects, orthopedic handicaps, heart disease including rheu-

matic fever. Special health problems around leprosy, muscular dystrophy, and tuberculosis are discussed, and the problems of the child with multiple handicaps, the homebound, and the hospitalized child are treated in separate chapters.

In the third volume "mental and emotional deviates" are taken up, including the intellectually gifted child, brain injuries, cerebral palsy, hemiplegia and epilepsy, emotional disturbances, juvenile delinquency and mental retardation. The special problems of the aged, the narcotic and the alcoholic conclude the book. A thorough index in the third volume covering the material of all three volumes facilitates the finding of material.

These three volumes will be an invaluable help to the physician who sees his child patient as a troubled person in society, who recognizes his responsibility as going beyond the cure of the specific illness or the diseased organ to include all other aspects of the child's health and welfare within the framework of his family and community, and who wishes to offer his children the resources and assistance of the numerous agencies existing in the community.

BOOKS RECEIVED

Die Eigenart der Kindlichen Hirntætigkeit. Vol. 2. By Albrecht Peiper. Price, Geb. DM 44.50. Pp. 588, with 172 illustrations. VEB Georg Thieme, Hainstr. 17/19 Aufgang C, Leipzig, Germany, July, 1956.

Foundations of Nutrition. Ed. 5. By Clara Mae Taylor, Grace Macleod, and Mary Swartz Rose. Price, not given. Pp. 620, with 128 photographs and 26 tables. The Macmillan Company, New York, 1956.

Handbook of Poisons. By Robert H. Dreisbach. Price, $3. Pp. 426, with numerous illustrations. Lange Medical Publications, Los Altos, Calif., 1955.

Treatment of the Child in Emotional Conflict. By Hyman S. Lippman. Price, $6. Pp. 298. The Blakiston Division, McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York 36, 1956.

Klinische Funktionsdiagnostik. By H. Kuchmeister, W. Bolt, H. Goldeck, and H. Hamm. Price, $11.80. Pp. 411, with 152 illustrations. Georg Thieme Verlag; In U. S. A., Intercontinental Medical Book Corporation, New York 16, 1956.

On the Early Development of Mind. By Edward Glover. Price, $7.50. Pp. 483. International Universities Press, 227 West 13 Street, New York 11, July, 1956.

Internal Secretions of the Pancreas. By G. E. W. Wolstenholme and Cecilia M. O'Connor. Price, $7. Pp. 292, with 100 illustrations. Little, Brown & Company, 34 Beacon St., Boston, 1956.

Ageing in Transient Tissues. By G. E. W. Wolstenholme and Elaine C. P. Millar. Price, $6.75. Pp. 263, with 96 illustrations. Little, Brown & Company, 34 Beacon St., Boston, 1956.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment 1956. By the American Medical Association. Price, $5.50. Pp. 661. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, June 15, 1956.

Die Pflege des gesunden und des kranken Kindes. By W. Catel. Price, $10. Pp. 665, with 336 illustrations. Georg Thieme Verlag, Intercontinental Medical Book Corporation, New York 16, July 27, 1956.

Sæuglings-Enteritis. By A. Adam, O. H. Braun, H. Hungerland, G. Ilgner, F. Kauffmann, H. W. Ocklitz, F. Orskov, E. F. Schmidt, D. Schreier, and R. Thurau. Price, $14.30. Pp. 534, with 43 illustrations. Georg Thieme Verlag, Intercontinental Medical Book Corporation, New York 16, July, 1956.

Of Water, Salt and Life. By Lakeside Laboratories, Inc. Price, $7.50. Pp. 72, with 31 illustrations. Lakeside Laboratories, Inc., Milwaukee 1, 1956.

Das Skelett des Kindes. By W. Swoboda. Price, $11.40. Pp. 184, with 199 illustrations. Georg Thieme Verlag, Intercontinental Medical Book Corporation, New York 16, July 19, 1956.

Practitioners' Conferences Held at New York Hospital—Cornell Medical Center. Edited by Claude E. Forkner. Price, not given. Pp. 406, with 9 illustrations. Appleton-Century-Crofts, Inc., New York, 1956.

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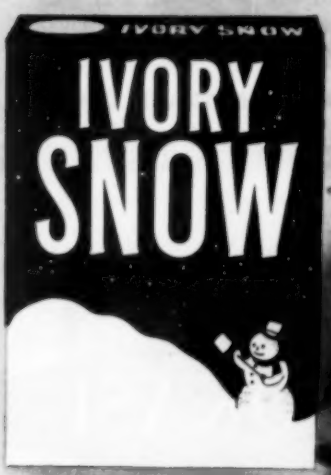

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*Shwachman, H., Children's Hospital, Boston; The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Butler, A., Harvard Medical School, private communication.

Kagan, B., Ill. Med. Jl. 107; 120, (1955).

Gibbs, G. E., Bradley, J. E., and Minor, J. V., Diagnosis and Treatment of Cystic Fibrosis of the Pancreas. J.A.M.A. 145: 1187 (1951).

Everson, T. C., Grossman, M. I., and Ivy, A. C.: Bulletin of Amer. College of Surgeons, January, 1950.

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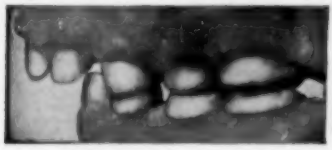

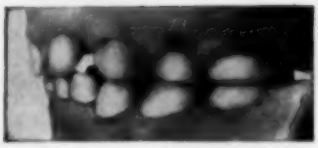

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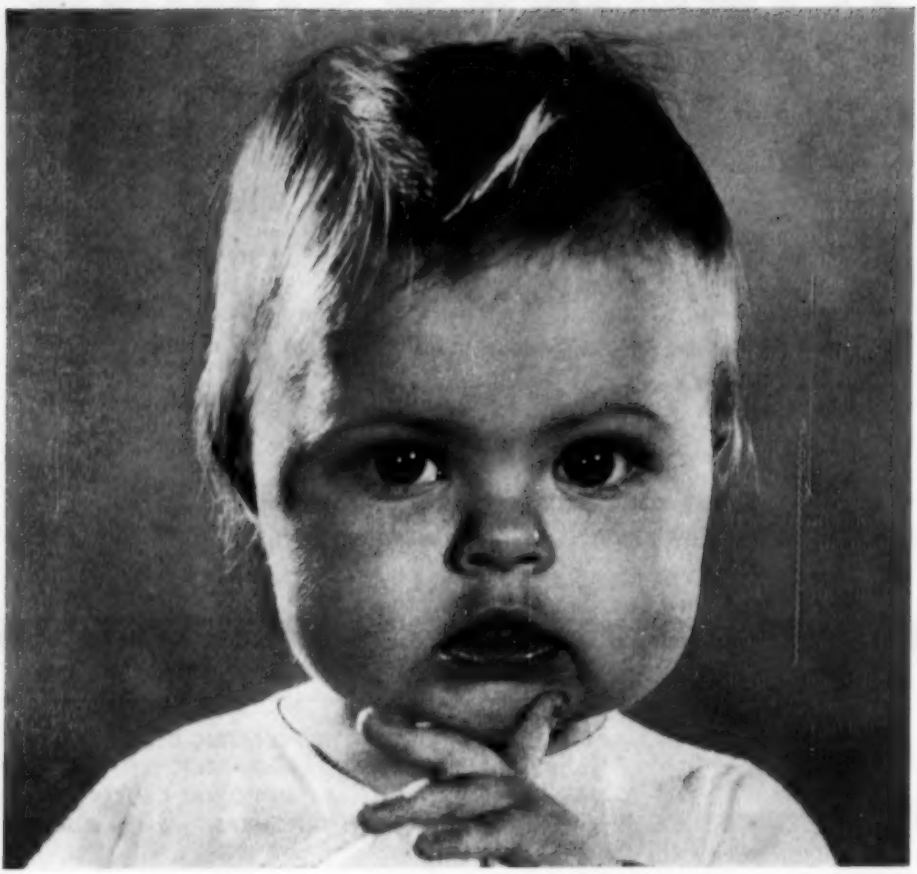

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1. Bowes, A. deP.: Dietotherapy—Nutrition of Children During Their School Years, Am. J. Clin. Nutrition *3*:254 (May-June) 1955.

2. Sebrell, W. H., Jr.: Trends and Needs in Nutrition, J.A.M.A. *150*:40 (May 2) 1953.

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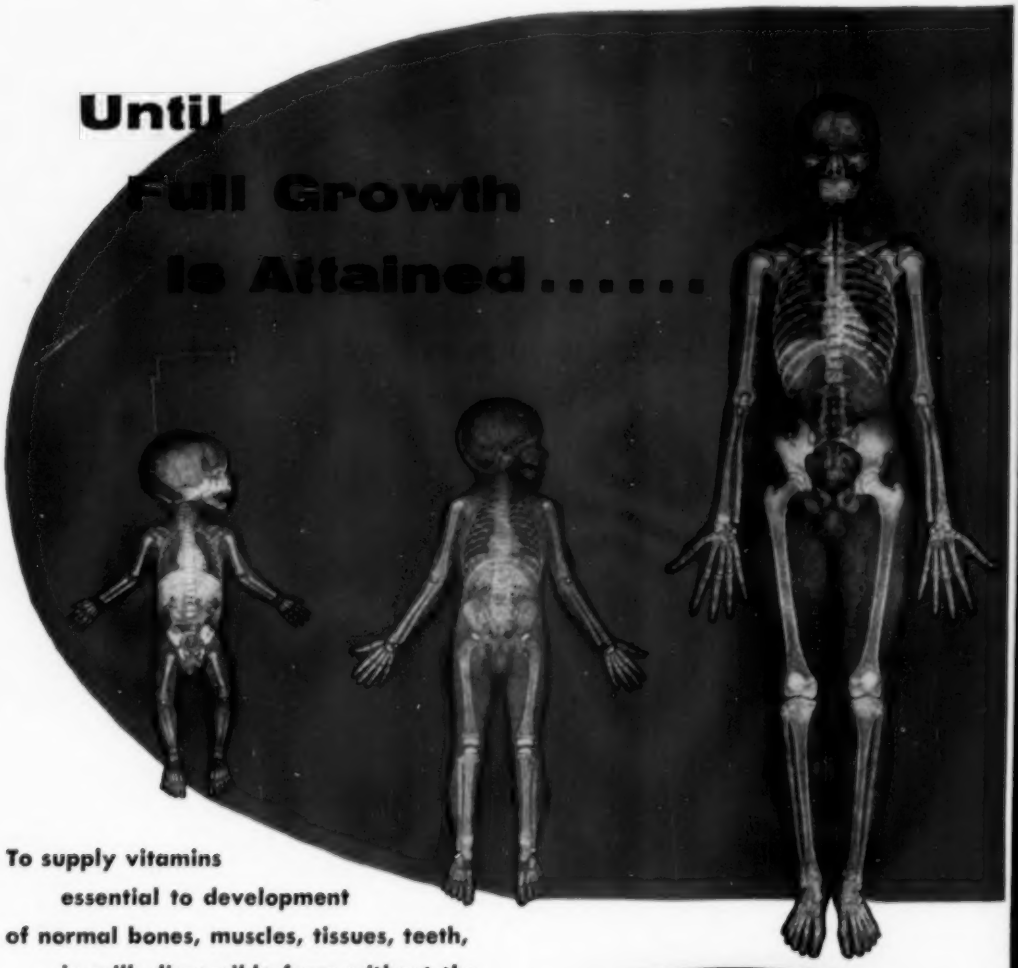

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